Total Syntheses of Eremophilane Sesquiterpenoids Based on Biogenetic Hypotheses

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Erlangung der naturwissenschaftlichen Doktorwürde
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Zürich, 2018

Für meine Familie

TABLE OF CONTENT

This PhD thesis is based on the following manuscripts and parts have been published similarly or identical:

Total Synthesis of the Sesquiterpenoid Periconianone A Based on a Postulated Biogenesis
R. Liffert, A. Linden, K. Gademann, *J. Am. Chem. Soc.* **2017**, *139*, 16096–16099.

Total Synthesis of the Polyoxygenated Sesquiterpenes Guignarderemophilanes C and D
R. Liffert, A. Ilazi, K. Gademann, *Helv. Chim. Acta* **2018**, doi:10.1002/hlca.201800011.

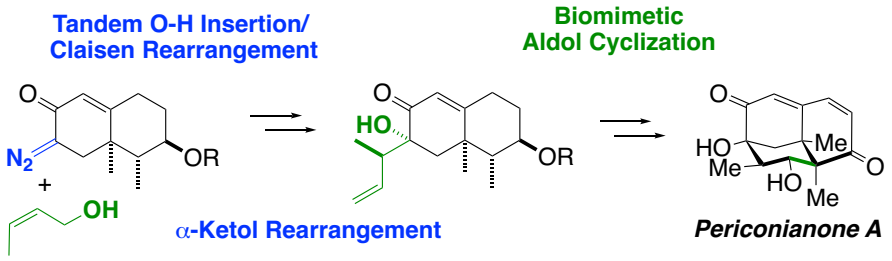
The Furan Shuffling Hypothesis: A Biogenetic Proposal for Eremophilane Sesquiterpenoids
R. Liffert, N. Lardon, A. Linden, K. Gademann, *manuscript in preparation.*

SUMMARY

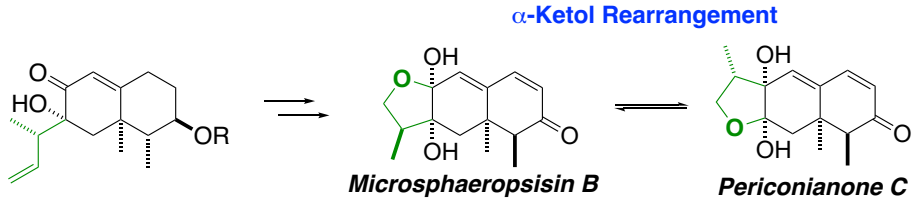
Nature has established highly effective ways to form structurally complex molecules, and the elegance of these biosynthetic routes has inspired preparative organic chemists in the past and today. This thesis encompasses synthetic studies on eremophilane sesquiterpenoids based on biogenetic hypotheses. The development of a divergent approach led to the successful total synthesis of six eremophilane-type natural products, none of which has been synthetically prepared before.

In **Chapter 1**, a general introduction presents eremophilane sesquiterpenes, their biosynthesis and strategies described in literature for the preparation of these natural products by organic synthesis. Eremophilanes are secondary metabolites structurally characterized by a decalin core unit with two one-carbon substituents at C4 and C5, and an isopropyl or isopropenyl group at C7. As their constitution cannot be rationalized by L. Ružička's *Isoprene Rule*, it is not surprising that the correct structural assignment of eremophilone, the first isolated and characterized member of the eremophilane family, was a seven-year process including several proposals that later turned out incorrect.

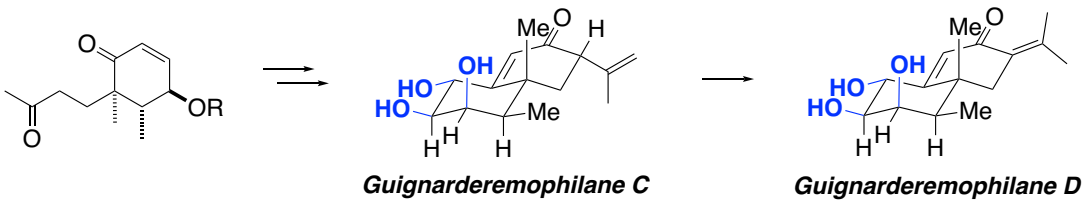
In **Chapter 2**, the first total synthesis of the complex tricarbocyclic sesquiterpenoid periconianone A based on a postulated biogenetic route is reported. Key elements of the enantioselective synthetic strategy include the use of an isopropenyl group as a removable directing group, a sequence featuring a Rh-mediated O−H insertion/[3,3]-sigmatropic rearrangement and subsequent α-ketol rearrangement, and a late stage aldol addition to furnish the complex cage-like framework.



Chapter 3 contains an account of the first enantioselective total syntheses of microsphaeropsisin B and C based on an intermediate from the total synthesis of periconianone A. In total, the synthesis of microsphaeropsisin B and C comprises a linear sequence of 15 steps starting from γ-hydroxy carvone. Mild reaction conditions for an α-ketol rearrangement did not only allow for conversion of microsphaeropsisin B into periconianone C, but also for the transition of microsphaeropsisin C into 4-*epi*-periconianone C. Based on the structural similarities of the recently isolated eremophilane-type sesquiterpenoids microsphaeropsisin B and C and the *iso*-eremophilane periconianone C, a revised biogenetic hypothesis for C8–C11-connected *iso*-eremophilanes is presented and corroborated by strong experimental evidence.



In **Chapter 4**, the total syntheses of the neural anti-inflammatory agents guignarderemophilane C and D are reported. The presented synthetic route proceeds *via* a diketone intermediate from the total synthesis of periconianone A. Key for the successful conversion of this intermediate into both targets was finding a suitable strategy to install the 1,2,3-trihydroxylated A-ring scaffold. For this purpose, a Mitsunobu inversion, epoxidation, and regioselective epoxide opening sequence has been effectively employed, before the bicyclic ring system was constructed by an aldol condensation reaction on a sterically demanding substrate.

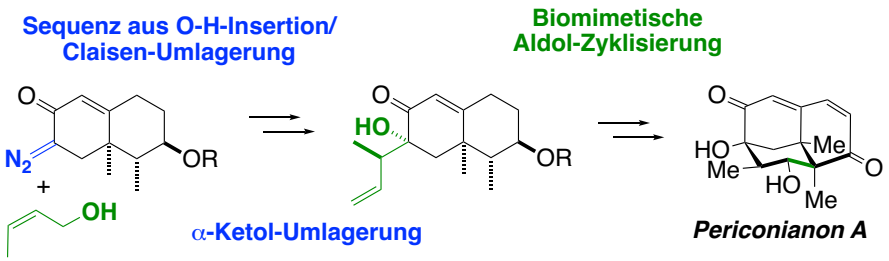


ZUSAMMENFASSUNG

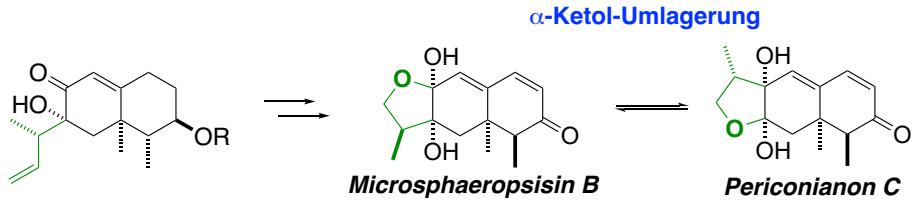
Strukturell komplexe Moleküle können in der Natur über hoch effiziente biosynthetische Pfade aufgebaut werden, deren Eleganz präparative organische Chemiker in der Vergangenheit und auch heute noch inspiriert. Diese Arbeit umfasst die Entwicklung von Synthesestrategien für Eremophilan-Sesquiterpenoide in Anlehnung an die vorgeschlagene biosynthetische Route. Einer divergenten Synthesestrategie folgend wurden sechs Naturstoffe aus der Familie der Eremophilane hergestellt, die so erstmalig durch Totalsynthese zugänglich wurden.

Im **ersten Kapitel** dieser Arbeit wird im Rahmen einer allgemeinen Einleitung die Naturstofffamilie der Eremophilan-Sesquiterpene vorgestellt, wobei im Besonderen auf deren Biosynthese sowie die bislang in der Literatur beschriebenen präparativen Arbeiten zur Laborsynthese dieser Naturstoffe eingegangen wird. Eremophilane sind Sekundärmetaboliten, die sich strukturell durch eine zentrale Decalin-Einheit mit zwei C_1-Substituenten an C4 und C5 sowie eine Isopropyl- oder eine Isopropenyl-Gruppe an Position C7 auszeichnen. Da ihre Konstitution sich nicht mithilfe von L. Ružičkas Isoprenregel erklären lässt, überrascht es nicht, dass die korrekte Strukturaufklärung von Eremophilon, dem ersten isolierten und charakterisierten Vertreter der Eremophilan-Naturstofffamilie, sieben Jahre in Anspruch nahm und in der Zwischenzeit mehrere Vorschläge veröffentlicht wurden, die sich nachher als nicht korrekt erwiesen.

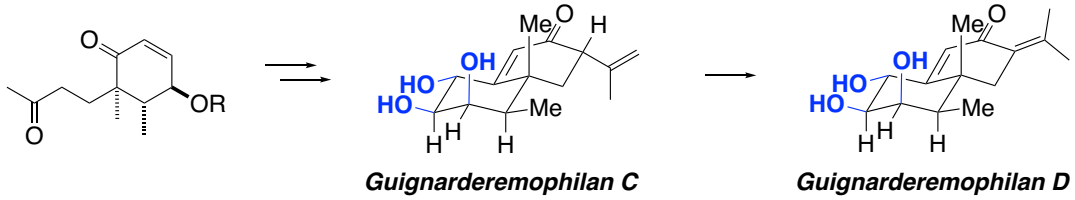
In **Kapitel 2** wird über die erste Totalsynthese des komplexen tricarbocyclischen Sesquiterpenoids Periconianon A basierend auf dem postulierten Biosynthesepfad berichtet. Besonders bemerkenswert an dieser enantioselektiven Synthese sind die Verwendung eines Isopropenyl-Substituenten als abspaltbare dirigierende Gruppe, eine Sequenz aus Rh-mediierter O–H-Insertion/[3,3]-sigmatroper Umlagerung und anschliessender α-Ketol-Umlagerung sowie eine Aldoladdition in der Endphase der Synthese, die das komplexe käfigartige Molekülgerüst schliesst.



Kapitel 3 beschreibt die erste enantioselektive Totalsynthese von Microsphaeropsisin B und C ausgehend von einem Intermediat aus der Totalsynthese von Periconianon A. Insgesamt umfasst die Synthese von Microsphaeropsisin B und C eine lineare Sequenz von 15 Schritten mit γ-Hydroxycarvon als Ausgangsstoff. Eine α-Ketol-Umlagerung unter milden Reaktionsbedingungen ermöglicht die Überführung von Microsphaeropsisin B in Periconianon C sowie von Microsphaeropsisin C in 4-*epi*-Periconianon C. In Hinblick auf die strukturellen Ähnlichkeiten zwischen den erst kürzlich isolierten Eremophilan-Sesquiterpenoiden Microsphaeropsisin B und C und dem *iso*-Eremophilan Periconianon C wird eine Revision der aktuellen Hypothese zur Biogenese für C8–C11-verknüpfte *Iso*-Eremophilane vorgeschlagen und durch die Ergebnisse aus unseren synthetischen Arbeiten untermauert.



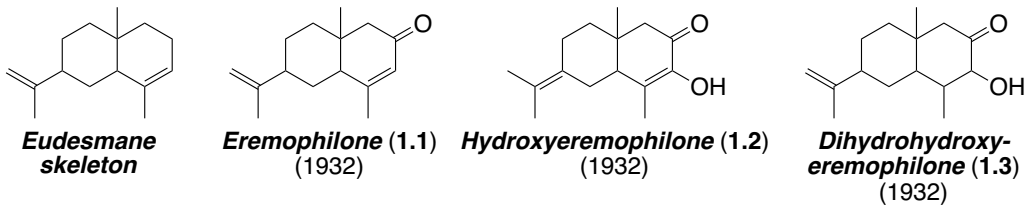
In **Kapitel 4** wird über die Totalsynthesen der anti-neuroinflammatorisch wirksamen Naturstoffe Guignarderemophilan C und D berichtet. Die vorgestellte Syntheseroute geht von dem Diketon-Intermediat aus der Periconianon A-Synthese aus. Ausschlaggebend für die erfolgreiche Synthese der beiden angestrebten Naturstoffe von diesem Intermediat aus war die Etablierung einer geeigneten Strategie zum Aufbau des 1,2,3-trihydroxylierten A-Rings. Um dieses Ziel zu erreichen, wurde eine Mitsunobu-Inversion sowie eine Epoxidierung mit anschliessender regioselektiver Ringöffnung durchgeführt, bevor eine intramolekulare Aldolkondensation dieses sterisch anspruchsvollen Substrats schliesslich zum Aufbau des bicyclischen Ringsystems führte.



1 EREMOPHILANE SESQUITERPENOIDS

1.1 Historical Background[1]

In 1932, A. E. Bradfield, A. R. Penfold and J. L. Simonsen reported on the first isolation of an eremophilane sesquiterpene from the wood oil of *Eremophila mitchellii*, a tall shrub or small tree endemic to the drier parts of New South Wales, Queensland and South Australia.[2] The highly viscous reddish-brown oil was obtained by steam distillation of the wood shavings. By extensive separation procedures, a crystalline ketone characterized by the molecular formula $C_{15}H_{22}O$ was isolated and named eremophilone (**1.1**). Two additional compounds were named 2-hydroxyeremophilone (**1.2**) and 2-hydroxy-1,2-dihydroeremophilone (**1.3**).



Eudesmane skeleton ***Eremophilone* (1.1)** (1932) ***Hydroxyeremophilone* (1.2)** (1932) ***Dihydrohydroxy-eremophilone* (1.3)** (1932)

Figure 1.1: Structure for eudesmane skeleton and proposed structures for eremophilone, hydroxyeremophilone and dihydrohydroxyeremophilone, as published in 1932.

In a primary report, it was suggested that eremophilone and its derivatives belong to the eudesmane family of sesquiterpenes and based on the following structural elucidation, structures **1.1**, **1.2** and **1.3** were proposed (Figure 1.1): dihydroeremophilol, obtained by reduction of eremophilone with sodium in ethanol, was dehydrogenated upon treatment with selenium to eudalene with loss of the angular methyl group, thus providing evidence for a bicyclic structure (Scheme 1.2). Dehydrogenation using sulfur[3] or selenium[4] had been a valuable method in studying the constitution of natural products and was introduced as well as pioneered to the terpene field by L. Ružička. He had shown that a number of sesquiterpenoids form cadalene or eudalene upon dehydrogenation. While cadalene contains fifteen carbon atoms, eudalene only comprises fourteen carbon atoms. It was suggested that sesquiterpenoids leading to both degradation compounds, cadalene and eudalene, are derived from the same

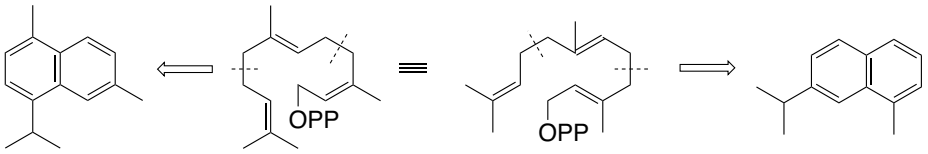
[1] For reviews: J. L. Simonsen, D. H. R. Barton, in The Terpenes, *Vol. III*, Cambridge University Press, **1961**, pp. 212-224; E. L. Ghisalberti, in Stud. Nat. Prod. Chem., *Vol. 15* (Ed.: A.-u. Rahman), Elsevier, **1995**, pp. 225-287; D. H. R. Barton, *Proc. Chem. Soc.* **1958**, 61-66.

[2] A. E. Bradfield, A. R. Penfold, J. L. Simonsen, *J. Chem. Soc.* **1932**, 2744-2759.

[3] L. Ružička, E. A. Rudolph, *Helv. Chim. Acta* **1927**, *10*, 915-920; L. Ružička, J. Meyer, M. Mingazzini, *Helv. Chim. Acta* **1922**, *5*, 345-368; L. Ružička, J. Meyer, *Helv. Chim. Acta* **1921**, *4*, 505-510.

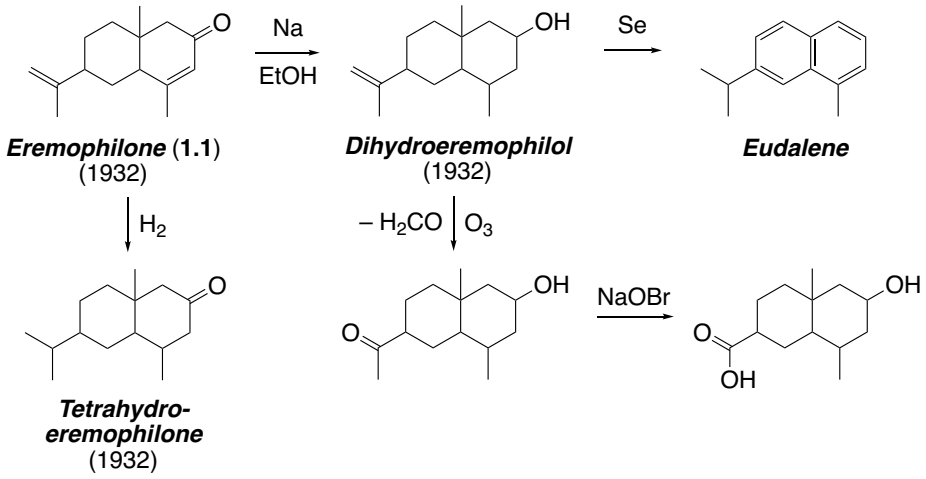
[4] L. Ružička, *Helv. Chim. Acta* **1936**, *19*, 419-423; L. Ružička, E. Peyer, *Helv. Chim. Acta* **1935**, *18*, 676-684.

farnesyl precursor, but differ in their constitution by the latter bearing an angular methyl group, which is cleaved from the carbon skeleton under the harsh reaction conditions applied (Scheme 1.1).



Scheme 1.1: Cadalene and eudalene as FPP derived sesquiterpenoid dehydrogenation products.

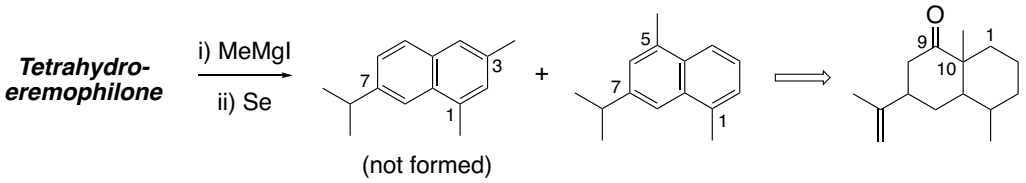
Formation of tetrahydroeremophilone upon hydrogenation indicated the presence of two double bonds in eremophilone. One of those double bonds was found to be incorporated in an isopropenyl side chain, established by ozonolysis of the terminal olefin of dihydroeremophilol to form a keto-alcohol and formaldehyde. The corresponding acid was then obtained by treatment of methyl ketone with sodium hypobromite. The presence of a CH_2 group next to the carbonyl was proven by the observation that eremophilone formed the crystalline hydroxymethylene derivative upon treatment with base and ethyl formate. On the other hand, the α,β-unsaturation next to the carbonyl group was disclosed by formation of an epoxide after treatment with hydrogen peroxide under basic conditions. The epoxide was opened by sodium acetate in acetic anhydride, and basic hydrolysis formed a diosphenol, which was identified as hydroxyeremophilone. To incorporate such an $R–CH_2–CO–CH=CR_2$ fragment in an eudesmane skeleton without the double bond of the isopropenyl group in conjugation, eremophilone was suggested to have the constitution given in Figure 1.1.



Scheme 1.2: Experiments for the structural assignment of eremophilone as reported in 1932.

Hydroxyeremophilone was shown to contain an isopropylidene side chain, as ozonolysis released acetone. Together with the finding that hydroxyeremophilone is accessible from eremophilone by oxidation, the structure given in Figure 1.1 was assigned. However, the origin of double bond isomerization leading to an isopropylidene side chain could not be explained at that time.

During structural elucidation of the sesquiterpenoid α-cyperone,[5] J. L. Simonsen and co-workers utilized a procedure involving Grignard methylation followed by dehydrogenation to locate the position of the carbonyl group. Applying the same procedure for eremophilone, *viz.* reaction of tetrahydroeremophilone with methylmagnesium iodide followed by treatment with selenium, formed 1,5-dimethylated – and not the anticipated 1,3-dimethylated – naphthalene derivative (Scheme 1.3).[6] Thus, the carbonyl group was proven to be at position C9 in eremophilone and not at position C2, as previously proposed. All the preliminary structural suggestions for **1.1**, **1.2** and **1.3** (Figure 1.1) were finally ruled out after reduction and dehydrogenation of the hydroxymethylene derivative of tetrahydroeremophilane formed 1,6-dimethyl-7-isopropylnaphthalene in a similar manner.



Scheme 1.3: Identification of the carbonyl group's position in eremophilone by Grignard methylation and dehydrogenation.

However, the combination of the earlier established R–CH_2–CO–CH=CR_2 fragment (C1=C10 unsaturation) with the finding that the included carbonyl group is located at position C9 in an eudesmane skeleton is invalid when C10 is a quaternary carbon atom. Therefore, J. L. Simonsen and co-workers proposed bicylco[4.6.0] systems for eremophilone and derivatives, before Sir R. Robinson suggested the position for the angular methyl group at C5 instead of C10 in a bicyclo[4.4.0] system. Hence, seven years after their first manuscript had been published, A. R. Penfold and J. L. Simonsen reported on revised structures for eremophilone and its congeners (Figure 1.2).[7]

[5] A. E. Bradfield, B. H. Hegde, B. S. Rao, J. L. Simonsen, A. E. Gillam, *J. Chem. Soc.* **1936**, 667-677.

[6] A. E. Bradfield, N. Hellstrom, A. R. Penfold, J. L. Simonsen, *J. Chem. Soc.* **1938**, 767-774.

[7] A. R. Penfold, J. L. Simonsen, *J. Chem. Soc.* **1939**, 87-89.

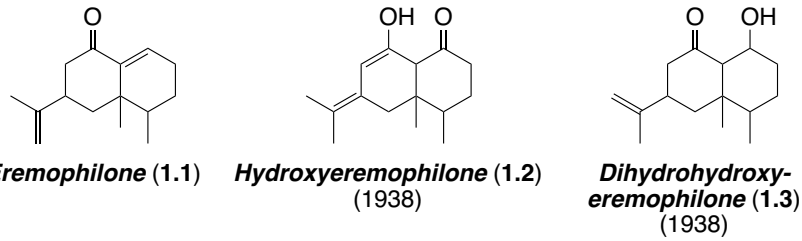
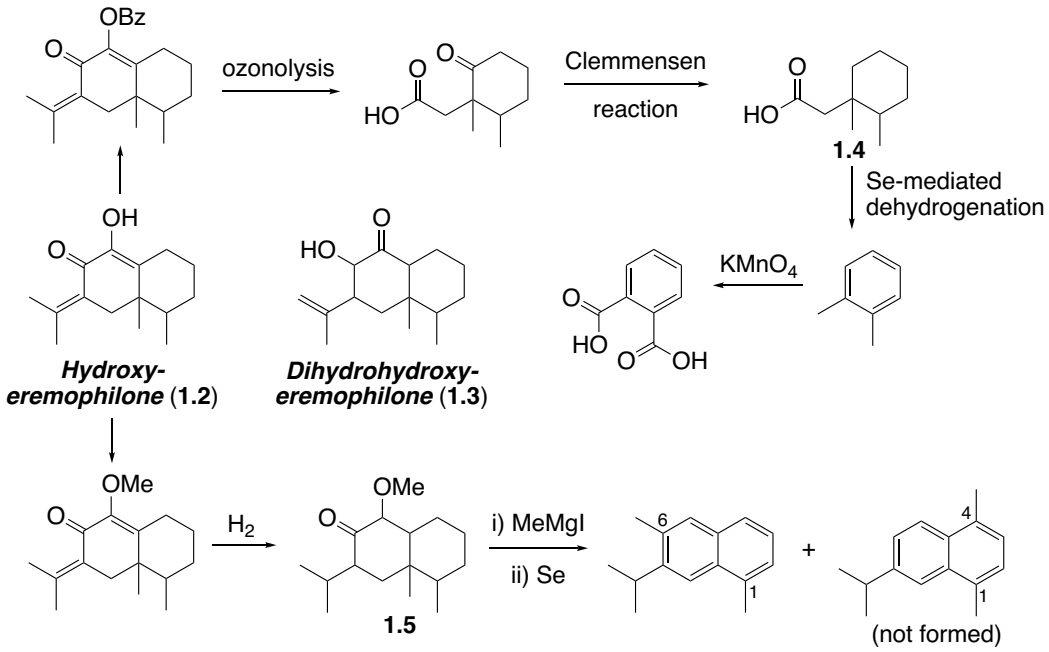


Figure 1.2: Structural formulae for eremophilone, hydroxyeremophilone and dihydrohydroxy-eremophilone as reported in 1938.

Indeed, the proposed structure of eremophilone (Figure 1.2) was later proven to be correct,[8] but the structures of hydroxyeremophilone as well as for dihydrohydroxyeremophilone were only partially correct. Evidence for the 1,2-dimethyl pattern was provided by ozonolysis of the benzoate of hydroxyeremophilone and subsequent Clemmensen reduction, which gave (1,2-dimethylcyclohexyl)acetic acid (**1.4**). Dehydrogenation of the methyl ester of **1.4** led to formation of *o*-xylene, which was oxidized to phthalic acid with potassium permanganate (Scheme 1.4).



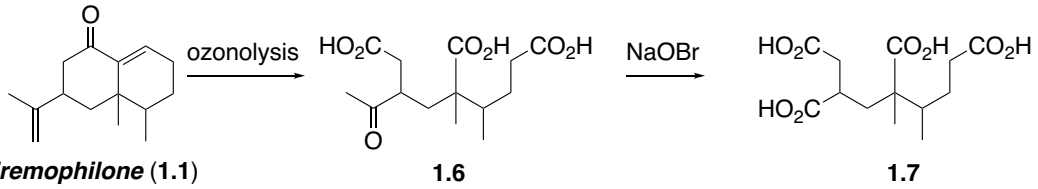
Scheme 1.4: Degradation of benzoylated hydroxyeremophilone for the positioning of the two methyl groups in eremophilone and its congeners; and of *O*-methylated hydroxyeremophilone to identify the location of the carbonyl group.

The proposed carbon skeleton of eremophilone, characterized by a methyl group at C5, challenged the isoprene rule, which was pioneered at that time and became of significant

[8] T. A. Geissman, *J. Am. Chem. Soc.* **1953**, *75*, 4008-4011.

validity.[9] When R. Robinson suggested to J. L. Simonsen the revised structures for eremophilone and derivatives, he anticipated this connectivity to have its origin in a methyl migration *via* a carbocation rearrangement in an isoprenoid eudesmane precursor. Although we are aware of methyl migrations and carbon skeleton rearrangements in terpene biosynthesis today, these suggestions were of surprising novelty at the time and can be considered as a milestone for subsequent investigations towards terpene biosynthetic hypotheses. As the first characterized structure of a naturally occurring sesquiterpene that violates the isoprene rule, L. Ružička stated in 1959 that "eremophilone caused a sensation".[10]

The correct structural elucidation for hydroxyeremophilone (**1.2**) was achieved after the hydrogenation product **1.5** of the methyl ether of hydroxyeremophilone had been observed to form the 1,6- and not the 1,4-dimethylated naphthalene derivative upon methylation and Se-mediated dehydrogenation (Scheme 1.4). Additional evidence for the position of the enone moiety was provided by ozonolysis of eremophilone, which resulted in the keto-triacid **1.6**, which was subsequently oxidized to the tetraacid **1.7** by treatment with sodium hypobromite (Scheme 1.5).



Scheme 1.5: Ozonolysis to substantiate the position of the carbonyl moiety in eremophilone.

The relative and absolute configuration of eremophilone, hydroxyeremophilone and dihydrohydroxyeremophilone has been established by optical rotatory dispersion (ORD)[11] and NMR spectroscopy[12] studies as well as single crystal X-ray analysis[13] and chemical synthesis.[14]

ORD studies by the group of C. Djerassi also revealed the B-ring of eremophilone to be in a twist-boat conformation, allowing the isopropenyl group at C7 to be in equatorial orientation in order to avoid 1,3-diaxial interaction with the methyl substituent at C5. The single

[9] L. Ružička, *Experientia* **1953**, *9*, 357-367.

[10] L. Ružička, *Proc. Chem. Soc.* **1959**, 341-376.

[11] L. H. Zalkow, F. X. Markley, C. Djerassi, *J. Am. Chem. Soc.* **1960**, *82*, 6354-6362; L. H. Zalkow, F. X. Markley, C. Djerassi, *J. Am. Chem. Soc.* **1959**, *81*, 2914-2915.

[12] L. H. Zalkow, A. M. Shaligram, S.-e. Hu, C. Djerassi, *Tetrahedron* **1966**, *22*, 337-350.

[13] D. Grant, *Acta Cryst.* **1957**, *10*, 498-504.

[14] C. Djerassi, R. Mauli, L. H. Zalkow, *J. Am. Chem. Soc.* **1959**, *81*, 3424-3429.

crystal X-ray analysis of dihydrohydroxyeremophilone showed the two rings to be arranged in a *cis*-manner, typical for steroidal compounds, and all substituents except the angular methyl group, in equatorial orientation (Figure 1.3).

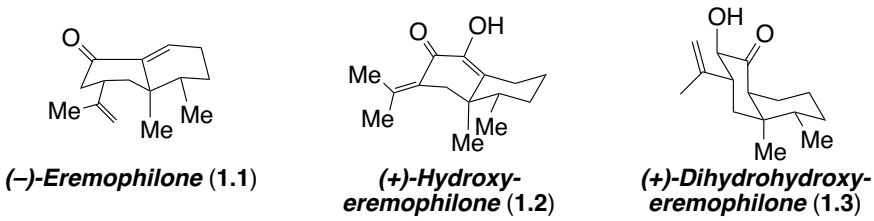
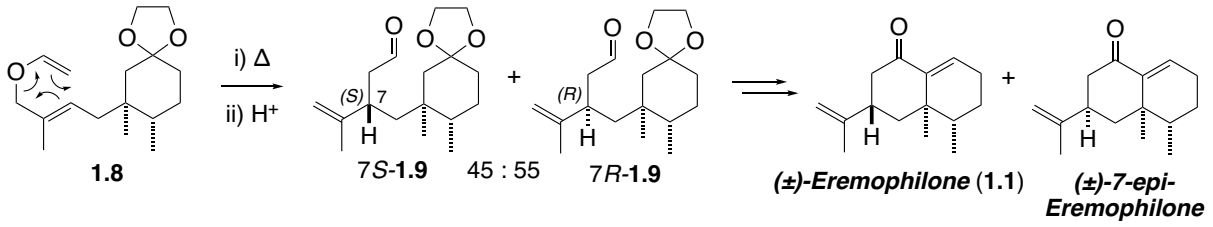


Figure 1.3: Absolute configuration of (–)-eremophilone, (+)-hydroxyeremophilone and (+)-dihydrohydroxyeremophilone.

The first successful total syntheses of (±)-eremophilone and its 7-*epi*-isomer were reported by F. E. Ziegler and P. A. Wender in 1974.[15] The main synthetic challenge was the installation of the two vicinal methyl groups at C4 and C5 in *cis*-orientation. Additionally, application of existing protocols for eremophilane synthesis based on Robinson annulation procedures accounted for the wrong oxidation pattern and were thus futile in this synthetic endeavor. The key step of the presented synthesis was Claisen rearrangement of the vinyl ether **1.8** to form a diastereomeric mixture of aldehydes 7*S*-**1.9** and 7*R*-**1.9** (Scheme 1.6). Subsequent aldolization and transposition of the C1 carbonyl group to C9 by Wharton rearrangement formed eremophilone and 7-*epi*-eremophilone. A stereoselective synthesis starting from β-pinene was presented by the group of J. E. McMurry in 1975.[16]



Scheme 1.6: First total synthesis of eremophilone by Claisen rearrangement and Wharton transposition as key steps.

[15] F. E. Ziegler, P. A. Wender, *Tetrahedron Lett.* **1974**, *15*, 449-452.

[16] J. E. McMurry, J. H. Musser, M. S. Ahmad, L. C. Blaszczak, *J. Org. Chem.* **1975**, *40*, 1829-1832.

1.2 Distribution and Classification of Eremophilane-Type Sesquiterpenoids

For almost 30 years, eremophilone, hydroxyeremophilone and dihydrohydroxyeremophilone had been the only isolated members of the eremophilane family of natural prodcuts.[17] In the last decades, however, more and more compounds were isolated and characterized with around 1500 eremophilanes known today (Reaxys search, 03/2018), primarily found in higher plants and fungi. In the plant kingdom, these sesquiterpenes are mainly present in the Asteraceae family, more precisely in the genera of *Ligularia*, *Senecio*, *Cacalia*, and *Petasites*, out of which the genus of *Ligularia* contains the most eremophilane-type natural products with more than 500 derivatives isolated from around 50 species.[18] While eremophilane-type compounds produced by plants had been known since the isolation of eremophilone in 1932; the first member isolated from a fungus was described four decades later by C. Riche *et al.* and named phomenone.[19] Today, there are about 150 eremophilanes isolated from fungi, and with a few exceptions compounds present in fungi are usually not found in plants or occur with the opposite absolute configuration.[20] Comprehensive reviews covering the structural diversity of eremophilanes isolated from plants[18,21] as well as from fungi[20] have been published recently.

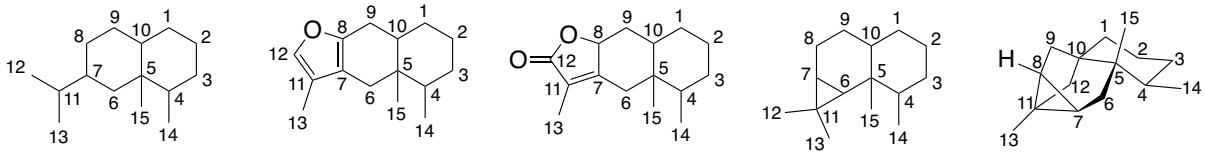


Figure 1.4: Structural types of bi-, tri- and tetracarbocyclic eremophilanes.

Structurally, eremophilane sesquiterpenes can be divided into compounds containing bi-, tri- or tetracarbocyclic skeletons (Figure 1.4). Bicarbocyclic eremophilanes can be classified based on the relative orientation of the alkyl substituents at C4, C5 and C7 and the location of the decalin double bond in their biogenetic precursors (Figure 1.5). The largest group of eremophilanes is supposed to be derived from eremophilene, which is characterized by a

[17] A. R. Pinder, A. K. Torrence, *J. Chem. Soc. C* **1971**, 3410-3414.

[18] L. Wu, Z. X. Liao, C. Liu, H. Y. Jia, J. Y. Sun, *Chem. Biodiversity* **2016**, *13*, 645-671.

[19] C. Riche, C. Pascard-Billy, M. Devys, A. Gaudemer, M. Barbier, J.-F. Bousquet, *Tetrahedron Lett.* **1974**, *15*, 2765-2766.

[20] K. T. Yuyama, D. Fortkamp, W. R. Abraham, *Biol. Chem.* **2018**, *399*, 13-28; R. Ebel, *Mar. Drugs* **2010**, *8*, 2340.

[21] C. J. Hou, M. Kulka, J. Z. Zhang, Y. M. Li, F. J. Guo, *Mini-Rev. Med. Chem.* **2014**, *14*, 664-677.

C1=C10 unsaturation and an all-*cis*-configuration of the three alkyl groups at C4, C5 and C7, which are – with few exceptions – β-orientated as in (–)-eremophilene or (–)-eremophilone. The decalin core of natural products derived from eremophilene is most often a saturated *cis*-fused ring system with minimal 1,3-diaxial interaction owing to the *cis*-relationship of the substituents at C5 and C7. Hence, eremophilanes with a *trans*-relation of the C4/C5 methyl groups to the C7 isopropyl/isopropenyl group, *i.e.* natural products derived from valencene or aristolochene, have either *trans*-fused rings or they are characterized by C9=C10 or C1=C10 unsaturation.

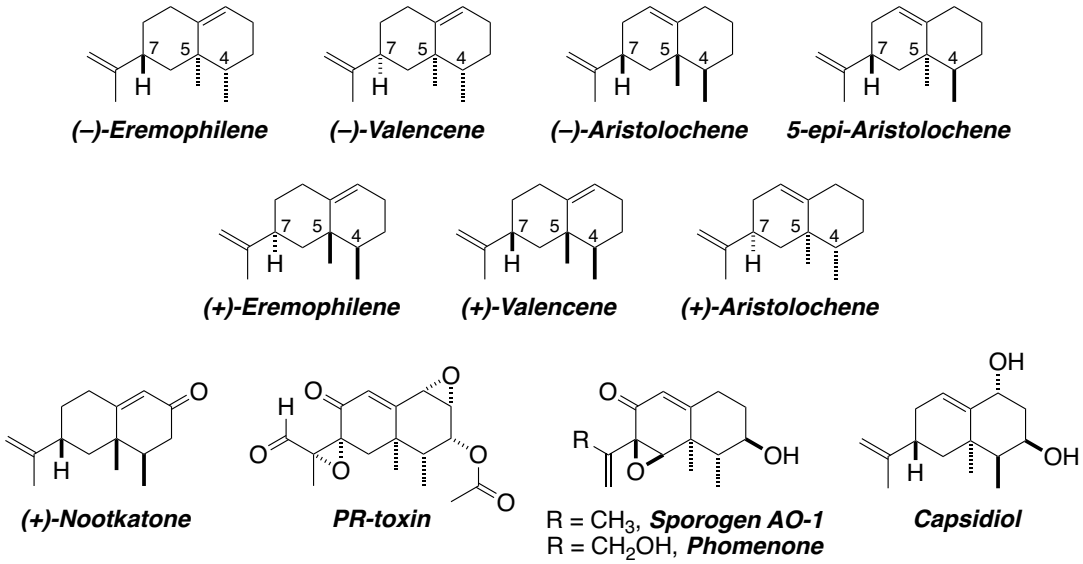


Figure 1.5: Structural precursors and prominent members of eremophilane sesquiterpenoids.

The growth-inhibiting compound (+)-valencene is widely distributed in the essential oils of citrus fruits and serves as a flavoring agent and aroma compound precursor in food industry.[22] Biosynthetically, one of the allylic oxidation products of (+)-valencene is (+)-nootkatone, known as the most important flavor of grapefruit and synthetically accessible by oxidation of (+)-valencene.[23] While the (–)-enantiomer of aristolochene was first isolated from the plant *Aristolochia indica* in 1970,[24] the (+)-enantiomer was obtained from fungi *Aspergillus terreus*[25] and *Penicillium roqueforti*.[26] Prominent eremophilanes derived from (+)-aristolochene are (1)

[22] J. Frohwitter, S. A. E. Heider, P. Peters-Wendisch, J. Beekwilder, V. F. Wendisch, *J. Biotechnol.* **2014**, *191*, 205-213.

[23] H. Erdtman, Y. Hirose, *Acta Chem. Scand.* **1962**, *16*, 1311-1314; M. Furusawa, T. Hashimoto, Y. Noma, Y. Asakawa, *Chem. Pharm. Bull.* **2005**, *53*, 1513-1514.

[24] T. R. Govindachari, P. A. Mohamed, P. C. Parthasarathy, *Tetrahedron* **1970**, *26*, 615-619.

[25] D. E. Cane, B. J. Rawlings, C.-C. Yang, *J. Antibiot.* **1987**, *40*, 1331-1334.

[26] T. M. Hohn, R. D. Plattner, *Arch. Biochem. Biophys.* **1989**, *272*, 137-143; A. A. Chalmers, A. E. de Jesus, C. P. Gorst-Allman, P. S. Steyn, *J. Chem. Soc., Perkin Trans. 1* **1981**, 2899-2903.

phomenone,[19,27] an oxygenated analog of sporogen AO-1, which was obtained from *Aspergillus oryzae*, an industrially relevant fungus in the production of soy sauce, and shows antifungal and phytotoxic activities;[28] and (2) PR-toxin, a mycotoxin isolated from *Penicillium roqueforti*, an ascomycete industrially used in the production of blue cheeses, such as Roquefort cheese, Gorgonzola or Blue Stilton.[29] Eremophilanes derived from 5-*epi*-aristolochene with a *trans*-relation of the methyl groups at C4 and C5 are rare with the most prominent member capsidiol, isolated from *Capsicum frutescens*[30] and *Nicotiana tabacum*.[31] Capsidiol is a phytoalexin, which is generated in response to fungal or viral infection.[32]

The regular bicyclic eremophilane motif often features an additional furan or lactone ring to give the corresponding furanoeremophilanes or eremophilenolides, respectively. Tricarbocyclic eremophilanes are, with a few exceptions, of the aristolane-type and characterized by the *gem*-dimethylcyclopropane unit fused across positions C6 and C7. The configuration of their three alkyl groups at C4, C5 and C7 is stereochemically related to valencane or its enantiomer by a *cis*-relation of the methyl groups and *trans* relation to the cyclopropane. Compounds bearing the ishwarane skeleton form the tetracarbocyclic class of eremophilanes and are characterized by fusion of the isopropenyl carbon atoms C11 and C12 with the decalin core at C7, C8 and C10.

1.3 Biosynthetic Pathway for the Formation of Eremophilane Sesquiterpenoids

Today, the biosynthesis of sesquiterpenes is well described to proceed *via* farnesyl pyrophosphate (FPP) as intermediate, which is formed by head-to-tail condensation of dimethylallyl diphosphate (DMAPP) with two equivalents of isopentenyl diphosphate (IPP), catalyzed by farnesyl pyrophosphate synthase. The enormous structural diversity within this class of terpenes with more than 10'000 known members results from sesquiterpene cyclases, which catalyze the formation of around 300 distinct 15-carbon skeletons. Although these

[27] T. Kitahara, H. Kiyota, H. Kurata, K. Mori, *Tetrahedron* **1991**, *47*, 1649-1654.

[28] S. Tanaka, K. Wada, S. Marumo, H. Hattori, *Tetrahedron Lett.* **1984**, *25*, 5907-5910; Y. Tirilly, J. Kloosterman, G. Sipma, J. J. Kettenes-Van Den Bosch, *Phytochemistry* **1983**, *22*, 2082-2083.

[29] R.-D. Wei, P. E. Still, E. B. Smalley, H. K. Schnoes, F. M. Strong, *Appl. Microbiol.* **1973**, *25*, 111-114.

[30] M. Gordon, A. Stoessl, J. B. Stothers, *Can. J. Chem.* **1973**, *51*, 748-752.

[31] J. A. Bailey, R. S. Burden, G. G. Vincent, *Phytochemistry* **1975**, *14*, 597.

[32] D. R. Threlfall, I. M. Whitehead, *Phytochemistry* **1988**, *27*, 2567-2580; I. M. Whitehead, D. R. Threlfall, D. F. Ewing, *Phytochemistry* **1989**, *28*, 775-779; R. Li, C.-S. Tee, Y.-L. Jiang, X.-Y. Jiang, P. N. Venkatesh, R. Sarojam, J. Ye, *Sci. Rep.* **2015**, *5*, 9682.

enzymes share a common mechanism of binding and ionization of FPP, the structural diversity is explained by a specific sequence of intramolecular cyclizations and rearrangements of the substrate while bound to the active site of the cyclase. As numerous reviews on sesquiterpene biosynthesis have been published,[33] this subchapter summarizes selected scientific results gathered over the last century, leading to the generally accepted biosynthetic pathway of eremophilane-type sesquiterpenoids.

As pointed out earlier, initial observations on the biogenesis of eremophilanes were provided by Sir R. Robinson, when he suggested that eremophilone, hydroxyeremophilone and dihydrohydroxyeremophilone differ from the structures of eudesmane-type sesquiterpenoids. He further proposed that the carbon skeleton of these three isolated natural products might be derived from an eudesmane precursor by methyl migration from C10 to C5. After the terpene rule had been introduced by O. Wallach[34] and found considerable affirmation in terpene biochemistry, this suggestion was disconcerting since the resulting skeleton after rearrangement cannot be explained by this general rule. Therefore, many research groups started to pursue this "hot topic" in order to validate Robinson's biogenetic hypothesis and to provide insights into the biosynthetic pathway of eremophilanes. In the beginning, different eudesmanes that might serve as model substrates for the 1,2-methyl shift to form the eremophilane-type skeleton have been proposed, but were not thoroughly or only unsuccessfully investigated.[11a,35]

In 1971, the group of R. G. Lawton hypothesized the involvement of spiro-intermediates in order to explain the origin of the stereochemical pattern in valencene- and aristolochene-derived eremophilanes (Scheme 1.7).[36] However, labeling studies of capsidiol using sodium [1,2-^{13}C]acetate as precursor in the biosynthesis and subsequent ^{13}C NMR experiments with the isolated compound ruled out a mechanism *via* spiro-intermediates and substantiated Robinson's proposition of a 1,2-methyl shift.[37]

---

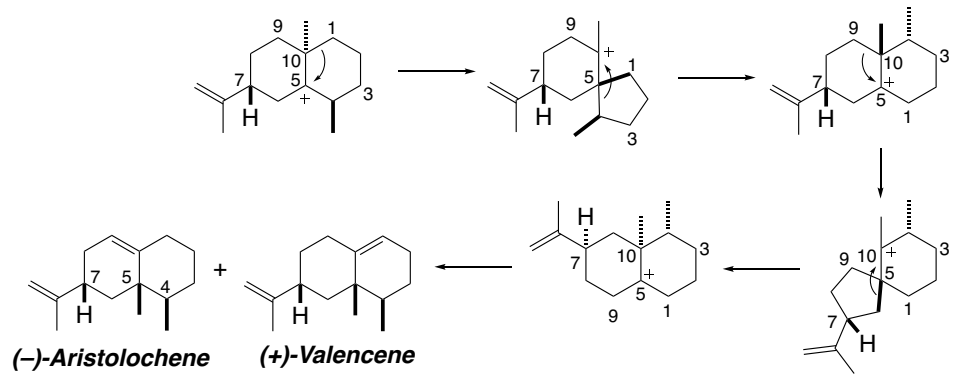
[33] For selected reviews: G. A. Cordell, *Chem. Rev.* **1976**, *76*, 425-460; J. S. Dickschat, *Nat. Prod. Rep.* **2011**, *28*, 1917-1936.

[34] O. Wallach, *Liebigs Ann. Chem.* **1887**, *238*, 78-89.

[35] J. W. Huffman, *J. Org. Chem.* **1972**, *37*, 2736-2739; C. H. Heathcock, Y. Amano, *Tetrahedron* **1968**, *24*, 4917-4921; C. H. Heathcock, T. R. Kelly, *Tetrahedron* **1968**, *24*, 3753-3765; G. Büchi, F. Greuter, T. Tokoroyama, *Tetrahedron Lett.* **1962**, *3*, 827-833; J. B. Hendrickson, *Tetrahedron* **1959**, *7*, 82-89.

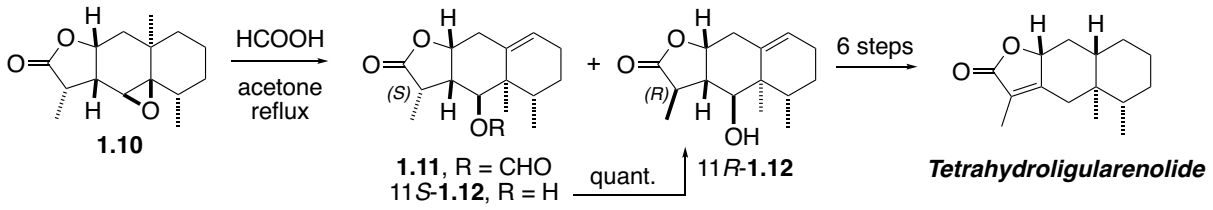
[36] R. G. Lawton, D. J. Dunham, *J. Am. Chem. Soc.* **1971**, *93*, 2075-2077.

[37] F. C. Baker, C. J. W. Brooks, S. A. Hutchinson, *J. Chem. Soc., Chem. Commun.* **1975**, 293b-294; F. C. Baker, C. J. W. Brooks, *Phytochemistry* **1976**, *15*, 689-694.



Scheme 1.7: Biogenetic hypothesis for the formation of valencene- or aristolochene-derived eremophilanes from eudesmane *via* spiro-intermediates proposed by the group of R. G. Lawton.

The first successful biomimetic transformation of an eudesmane- to an eremophilane-type sesquiterpenoid dates back to 1972.[38] When a mixture of eudesmanolide epoxide **1.10** and formic acid in acetone was heated to reflux, the C5-methylated eremophilanolides **1.11** and 11*S*-**1.12** were formed in 10 % and 34 % yield, respectively (Scheme 1.8). Besides five other minor compounds, side-product 11*R*-**1.12** featuring isomerization of the methyl group at C11 was isolated in 2 % yield. This isomerization was also initiated by stirring 11*S*-**1.12** with K_2CO_3 in toluene. In order to validate the structure of **1.12**, the obtained compound was converted to the known tetrahydroligularenolide in six steps.



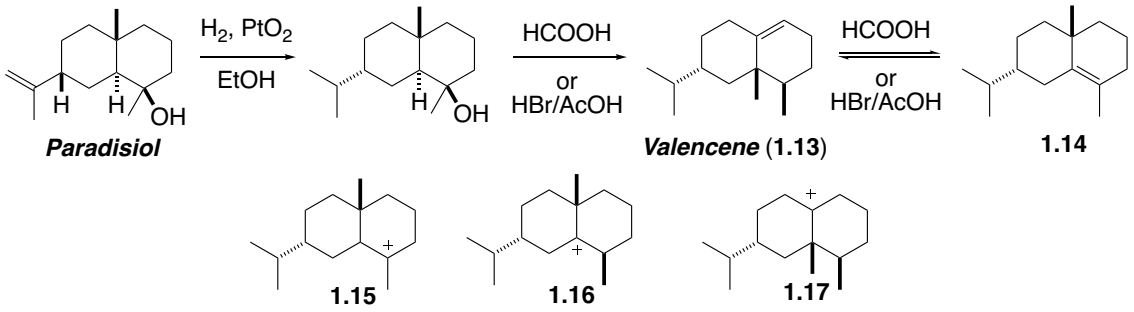
Scheme 1.8: First reported reaction involving a 1,2-methyl shift from C10 to C5 in an eudesmane sesquiterpenoid in order to provide evidence for the proposed biogenetic route.

In 1977, the group of A. R. Pinder reported on the *in vitro* and *in vivo* rearrangement of eudesmanes to eremophilanes.[39] After the C11=C12 double bond of paradisiol had been hydrogenated, treatment with either formic acid or hydrogen bromide in acetic acid gave valencene (**1.13**) (Scheme 1.9). The same rearrangement product was formed when tetrasubstituted olefin **1.14** was subjected to identical reaction conditions. Moreover, eremophilane **1.13** was synthesized from nootkatone in four steps and resulted in the identical

[38] I. Kitagawa, H. Shibuya, H. Takeno, T. Nishino, I. Yosioka, *Chem. Pharm. Bull.* **1976**, *24*, 56-60; I. Kitagawa, Y. Yamazoe, H. Shibuya, R. Takeda, H. Takeno, I. Yoshioka, *Chem. Pharm. Bull.* **1974**, *22*, 2662-2674; I. Kitagawa, H. Shibuya, Y. Yamazoe, H. Takeno, I. Yosioka, *Tetrahedron Lett.* **1974**, *15*, 111-114; I. Kitagawa, Y. Yamazoe, R. Takeda, I. Yosioka, *Tetrahedron Lett.* **1972**, *13*, 4843-4846.

[39] C. A. Miller, A. R. Pinder, *J. Chem. Soc., Chem. Commun.* **1977**, 230-231.

mixture of **1.13** and **1.14** when submitted to the conditions initiating the 1,2-shift. Therefore, it has been suggested that carbocation intermediates **1.15**, **1.16** and **1.17** might be involved in the rearrangement process.



Scheme 1.9: Experiments hinting at the involvement of carbocation intermediates in the biosynthesis of eremophilanes.

In an *in vivo* experiment, a suspension of [3-^{14}C]-labeled paradisiol in phosphate buffer and Triton X-100 was injected into unripe grapefruit and the fruits were exposed to sunlight for eight days. ^{14}C-Labeled valencene was isolated with an incorporation of 0.02 % ^{14}C.

In 1989, P. Ceccherelli *et al.* reported on the acid-catalyzed rearrangement of 3-keto-4,5-epoxy eudesmane.[40] Based on the observed co-occurrence of cyperanic acid and costic acid (Figure 1.6) in the Mediterranean plant *Dittrichia viscosa*,[41] they proposed a biogenetic relationship between these natural products. In order to study this hypothesis, 3-keto-4,5-epoxy eudesmanes 4*S*5*S*-**1.18** and 4*R*5*R*-**1.18** were synthesized.

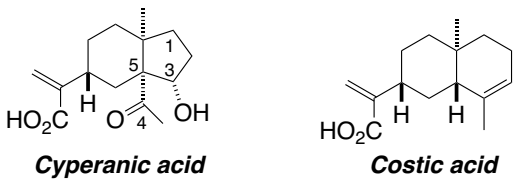


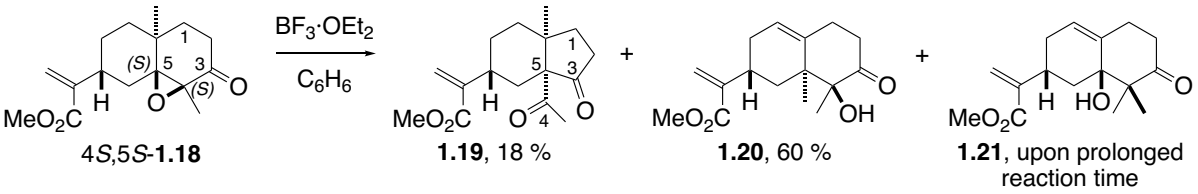
Figure 1.6: Structures of cyperanic acid and costic acid.

Treatment of 4α,5α-epoxy eudesmane **1.18** with $BF_3 \cdot OEt_2$ induced either a methylene shift to form the 5/6-bicyclic cyperane **1.19** by ring contraction in 18 % yield or a 1,2-methyl shift to form eremophilane-type compound **1.20** in 60 % yield (Scheme 1.10). Stirring the

[40] P. Ceccherelli, M. Curini, M. C. Marcotullio, O. Rosati, *Tetrahedron* **1989**, *45*, 3809-3818.

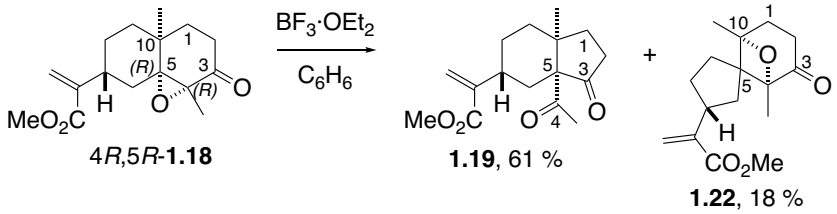
[41] P. Ceccherelli, M. Curini, M. C. Marcotullio, A. Menghini, *J. Nat. Prod.* **1988**, *51*, 1006-1009.

mixture of 4*S*5*S*-**1.18** and Lewis acid for 20 min instead of only 5 min, led to formation of C4-dimethylated product **1.21**.



Scheme 1.10: Rearrangement of 3-keto-4α,5α-epoxy eudesmane to cyperane- (**1.19**) and eremophilane-type (**1.20**) structures.

Diverging results were obtained when 4β,5β-epoxy eudesmane **1.18** was subjected to the same reaction conditions. Eremophilane **1.20** was not formed, instead a mixture of cyperane **1.19** and spirovetivane **1.22** was obtained in 61 % and 18 % yield, respectively (Scheme 1.11). These results suggested that cyperanes, eremophilanes and spirovetivanes are derived from an oxygenated eudesmane precursor.



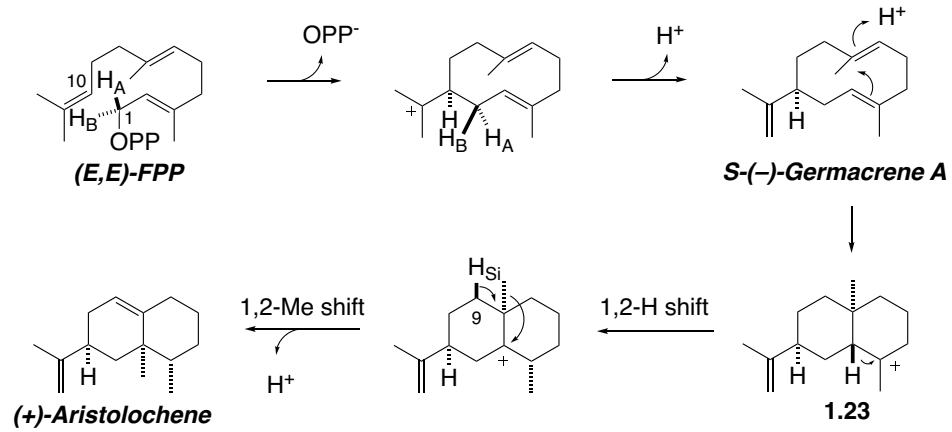
Scheme 1.11: Rearrangement of 3-keto-4β,5β-epoxy eudesmane to cyperane- (**1.19**) and spirovetivane-type (**1.22**) structures.

While most of the earlier biosynthetic studies on terpenes had been carried out on the cellular level by incorporation experiments using isotopically labeled precursors, investigations on the cell-free level in the sesquiterpene research field started in the 1990's and were mainly pioneered by the group of D. E. Cane.[42] Classical feeding experiments with intact organisms mainly suffered from poor uptake of the labeled precursors. In contrast, a cell-free system eliminates the natural cellular barriers for uptake and thus helped to create a better understanding of biosynthetic pathways. The isolation and characterization of several sesquiterpene cyclases and their application in both crude and purified form led to the formulation and corroboration of terpene biosynthetic mechanisms.[43]

[42] For reviews: D. E. Cane, *Chem. Rev.* **1990**, *90*, 1089-1103; G. A. Cordell; J. Degenhardt, T. G. Köllner, J. Gershenzon, *Phytochemistry* **2009**, *70*, 1621-1637.

[43] For review: D. W. Christianson, *Chem. Rev.* **2017**, *117*, 11570-11648.

In 1990, the group of D. E. Cane reported experiments performed with purified aristolochene synthase, which was isolated from cell-free extracts of the fungi *Aspergillus terreus*[26b] and *Penicillium roqueforti*.[32a] The proposed biosynthetic mechanism of this enzyme is shown in Scheme 1.12: ionization by cleavage of the pyrophosphate group from (*E,E*)-FPP, is followed by 1,10-cyclization and deprotonation to form *S*-(–)-germacrene A. Another protonation at C1 induces cyclization to the 10β-*trans*-eudesmane cation **1.23**. Sequential 1,2-hydride and 1,2-methyl shifts with deprotonation at C9 finally releases (+)-aristolochene. Initial experiments to provide evidence for this mechanism consisted in incubation of crude aristolochene synthase obtained from *Aspergillus terreus* with [12,13-^{14}C]-labeled FPP[44] as well as [11,12-^{13}C]- and [11,13-^{13}C]-FPP. The stereochemical course, however, was examined by separate incubation of 1*R*- and 1*S*-[1-^{2}H]FPP (H_A/H_B) with aristolochene synthase, which revealed the initial 1,10-cyclization to proceed with inversion of configuration at C1. Additional labeling experiments showed that deprotonation after the initial cyclization step takes place at the terminal *cis*-methyl group (C12) to form *S*-germacrene A and the final deprotonation proceeds by abstraction of H_{Si} at C9.[45] There is evidence that germacrene A is an intermediate in the cyclization process and that none of the intermediates is released from the active site in the enzymatic process forming (+)-aristolochene from FPP.[46]



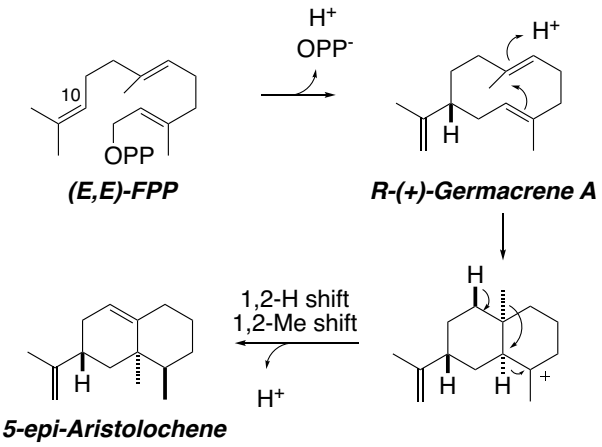
Scheme 1.12: Proposed biogenetic pathway for the synthesis of (+)-aristolochene.

[44] D. E. Cane, P. C. Prabhakaran, E. J. Salaski, P. H. M. Harrison, H. Noguchi, B. J. Rawlings, *J. Am. Chem. Soc.* **1989**, *111*, 8914-8916.

[45] D. E. Cane, P. C. Prabhakaran, J. S. Oliver, D. B. McIlwaine, *J. Am. Chem. Soc.* **1990**, *112*, 3209-3210.

[46] D. E. Cane, C. Bryant, *J. Am. Chem. Soc.* **1994**, *116*, 12063-12064; D. E. Cane, Y. S. Tsantrizos, *J. Am. Chem. Soc.* **1996**, *118*, 10037-10040.

In a similar manner, the biosynthetic pathway of 5-*epi*-aristolochene was profoundly investigated.[42a,47] The proposed mechanism catalyzed by *epi*-aristolochene synthase, shown in Scheme 1.13, is similar to the one suggested for aristolochene synthase, but leads to a different stereoisomer of the eremophilane-type skeleton.



Scheme 1.13: Proposed biogenetic pathway for the synthesis of 5-*epi*-aristolochene.

The identification of biosynthetic gene clusters by sequencing efforts and the recent advances in biomolecular techniques enabled heterologous expression and *in vitro* incubation studies using purified enzymes in order to investigate biogenetic pathways.[48] Gene clusters in different organisms encoding for valencene,[49] aristolochene, *epi*-aristolochene or eremophilene synthases have been identified. Further, enzymes responsible for oxidation of the sesquiterpene carbon skeleton have been discovered, *e.g.* several cytochrome P450 mono-oxygenases[50] responsible for the oxidation of (+)-valence to (+)-nootkatone. Due to the importance of (+)-nootkatone to flavor and fragrance industry and its large-scale production from the more abundant (+)-valencene, its biosynthetic pathway has been thoroughly investigated.

Very recently, the research groups of J. Dickschat and M. Christmann reported on the isolation of the sesquiterpene cyclase STC3 from the rice pathogenic fungus *Fusarium fujikuroi*, which was expressed in *Escherichia coli* and produced (+)-eremophilene upon

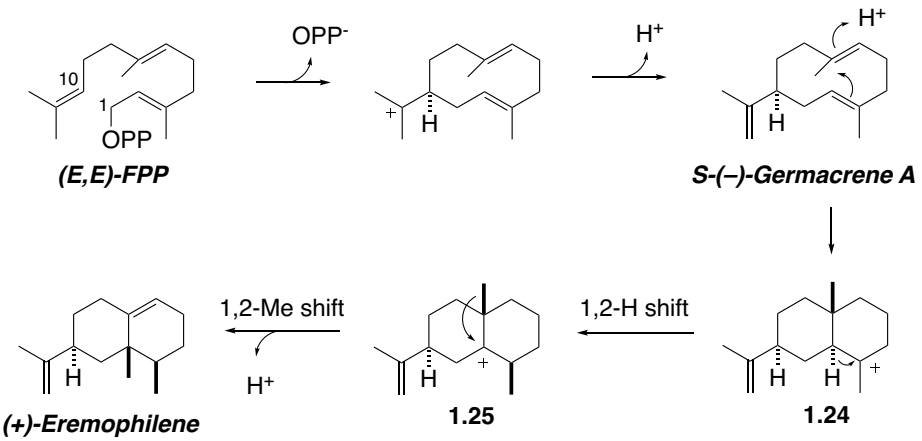
[47] K. A. Rising, C. M. Starks, J. P. Noel, J. Chappell, *J. Am. Chem. Soc.* **2000**, *122*, 1861-1866; D. J. Schenk, C. M. Starks, K. R. Manna, J. Chappell, J. P. Noel, R. M. Coates, *Arch. Biochem. Biophys.* **2006**, *448*, 31-44; J. A. Faraldos, Y. Zhao, P. E. O'Maille, J. P. Noel, R. M. Coates, *ChemBioChem* **2007**, *8*, 1826-1833.

[48] For recent review: J. S. Dickschat, *Eur. J. Org. Chem.* **2017**, 4872-4882.

[49] J. Lücker, P. Bowen, J. Bohlmann, *Phytochemistry* **2004**, *65*, 2649-2659.

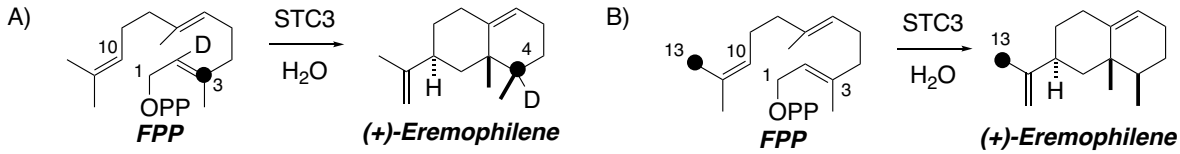
[50] R. J. Sowden, S. Yasmin, N. H. Rees, S. G. Bell, L.-L. Wong, *Org. Biomol. Chem.* **2005**, *3*, 57-64; A. Seifert, S. Vomund, K. Grohmann, S. Kriening, V. B. Urlacher, S. Laschat, J. Pleiss, *ChemBioChem* **2009**, *10*, 853-861; K. Cankar, A. van Houwelingen, D. Bosch, T. Sonke, H. Bouwmeester, J. Beekwilder, *FEBS Lett.* **2011**, *585*, 178-182.

incubation with FPP.[51] The proposed mechanism of eremophilene biosynthesis is almost identical to those described for aristolochene and *epi*-aristolochene and is summarized in Scheme 1.14. Enzymatic conversion of [2-^{2}H,3-^{13}C]-labeled FPP and ^{13}C-NMR analysis of the formed eremophilene showed deuterium incorporated at position C4 of eremophilene (Scheme 1.15, A). This observation substantiates a 1,2-hydride shift from C5 to C4 (**1.24** → **1.25**) in the proposed mechanism.



Scheme 1.14: Proposed biogenetic pathway for the synthesis of (+)-eremophilene.

Moreover, when D_2O was used as solvent for this reaction, no deuterium uptake was observed. Therefore, it was suggested that the same proton is involved in protonation of germacrene A and deprotonation to form (+)-eremophilene. When [13-^{13}C]-labeled FPP was used in the enzymatic reaction, incorporation of ^{13}C was only observed at C13 and not at C12 of (+)-eremophilene, explaining the stereochemical behavior of the terminal methyl groups in FPP in the process.



Scheme 1.15: Enzymatic conversion of FPP in the presence of the sesquiterpene cyclase STC3. A) [2-^{2}H,3-^{13}C]-labeled FPP was used, B) [13-^{13}C]-labeled FPP was used; black dots represent ^{13}C-isotopes.

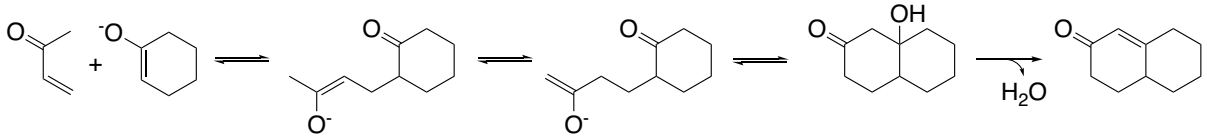
[51] I. Burkhardt, T. Siemon, M. Henrot, L. Studt, S. Rösler, B. Tudzynski, M. Christmann, J. S. Dickschat, *Angew. Chem. Int. Ed.* **2016**, *55*, 8748-8751.

1.4 Synthetic Contributions over the last Decades

An overview covering eremophilane syntheses up to 1977 is given in the book chapter "The Chemistry of the Eremophilane and Related Sesquiterpenes" in "Progress in the Chemistry of Organic Natural Products" by A. R. Pinder.[52] Therefore, the following subsections mainly deal with eremophilane syntheses reported in the last 40 years and the focus primarily lies on the categorization and exemplification of strategies elaborated on the construction of the bicyclic 6/6 carbon skeleton.

1.4.1 Robinson Annulation Procedures

Bicyclic 6/6 diketones are versatile building blocks and have been used as intermediates in the construction of numerous steroids and terpenoids like taxol.[53] A widely used synthetic method to prepare these decalones is the Robinson annulation, a tandem process of Michael addition followed by aldol condensation, which was first introduced by Sir R. Robinson and W. S. Rapson in 1935 (Scheme 1.16).[54,55]



Scheme 1.16: Robinson annulation mechanism for the construction of bicyclic 6/6 octalones.

Condensation of cyclohexanone with styryl methyl ketone under basic conditions gave the phenyl substituted octalone **1.26** in 43 % yield (Scheme 1.17, A). However, in the same year, the group of R. Robinson reported limitations of their procedure: octalone **1.27** was formed in only 15–20 % yield, when α-methylated cyclohexanone and 4-chloro-2-butanone were used in the reaction (Scheme 1.17, B).[56] The authors already recognized that the combination of a substituted cyclohexanone and methyl vinyl ketone, which was expected to

[52] A. R. Pinder, in Progress in the Chemistry of Organic Natural Products, *Vol. 34* (Eds.: W. Herz, H. Grisebach, G. W. Kirby), Springer-Verlag, Wien, **1977**, pp. 81-186.

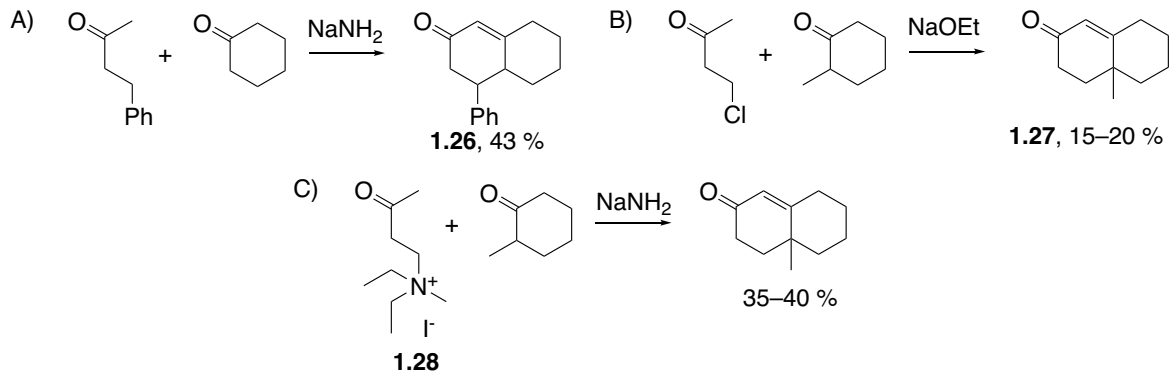
[53] For examples: W. S. Cheung, H. N. C. Wong, *Tetrahedron* **1999**, *55*, 11001-11016; S. Danishefsky, P. Cain, *J. Am. Chem. Soc.* **1976**, *98*, 4975-4983; S. J. Danishefsky, J. J. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn, M. J. Di Grandi, *J. Am. Chem. Soc.* **1996**, *118*, 2843-2859; K.-i. Fuhshuku, N. Funa, T. Akeboshi, H. Ohta, H. Hosomi, S. Ohba, T. Sugai, *J. Org. Chem.* **2000**, *65*, 129-135; T. Nagamitsu, T. Sunazuka, R. Obata, H. Tomoda, H. Tanaka, Y. Harigaya, S. Omura, A. B. Smith, *J. Org. Chem.* **1995**, *60*, 8126-8127; A. Pemp, K. Seifert, *Tetrahedron Lett.* **1997**, *38*, 2081-2084; A. B. Smith, J. Kingery-Wood, T. L. Leenay, E. G. Nolen, T. Sunazuka, *J. Am. Chem. Soc.* **1992**, *114*, 1438-1449.

[54] W. S. Rapson, R. Robinson, *J. Chem. Soc.* **1935**, 1285-1288.

[55] For review: F. Gallier, A. Martel, G. Dujardin, *Angew. Chem. Int. Ed.* **2017**, *56*, 12424-12458.

[56] E. C. du Feu, F. J. McQuillin, R. Robinson, *J. Chem. Soc.* **1937**, 53-60.

be rapidly formed by elimination of HCl from 4-chloro-2-butanone, was not ideally suited for this process. This general problem can be explained by the similar basicities of vinyl carbonyl compounds and the enolates obtained by deprotonation of the cyclic monoketones, resulting in the competitive polymerization reaction of the former.



Scheme 1.17: Different substitution pattern for both substrates in the Robinson annulation reaction.

Therefore, the modification of both the vinyl carbonyl Michael acceptor and the cyclohexanone were investigated to extend the scope of the Robinson annulation.[56] It was found that the reaction with quaternary Mannich base **1.28** gave increased yields of 35–40 % (Scheme 1.17, C) due to slow release of vinyl ketone under basic conditions by Hofmann elimination, thus keeping the Michael acceptor reagent at a low concentration. Using cyclohexanone compounds that are activated in the α-position, *e.g.* 1,3- dicarbonyl compounds or β-keto esters, yields were further improved. The growing interest in this reaction, not only in the context of eremophilane total synthesis, led to substantial progress in the development of new Robinson annulation procedures. While methodological optimization today mainly focusses on improvements of the diastereo- or enantioselectivity, initial research was primarily concentrated on obtaining the desired reactivity pattern and chemoselectivity with acceptable yields. Especially in the case of sterically demanding substrates like 2,3-disubstituted cyclohexanones, the original Robinson annulation protocol often gave low yields of the desired products due to the lack of regio- and stereoselectivity.[17,57] It is therefore not surprising that the Robinson annulation procedure was already highly investigated in early eremophilane syntheses for establishing the characteristic vicinal *cis*-methyl functionality (C4/C5).[58]

[57] C. Berger, M. Franck-Neumann, G. Ourisson, *Tetrahedron Lett.* **1968**, *9*, 3451-3452; E. Piers, R. W. Britton, W. Dewaal, *Can. J. Chem.* **1969**, *47*, 4307-4312.

[58] J. A. Marshall, T. M. Warne, *J. Org. Chem.* **1971**, *36*, 178-183; H. C. Odom, A. R. Pinder, *J. Chem. Soc. D* **1969**, 26-27; M. Pesaro, G. Bozzato, P. Schudel, *Chem. Commun. (London)* **1968**, 1152-1154; J. A. Marshall,

1.4.1.1 Modification of Cyclohexanone

While addition of Michael acceptors at the less substituted α-position of the carbonyl group can be carried out efficiently *via* enamine catalysis, the reaction at the more substituted position often results in polymerization of the vinyl carbonyls. In order to address those higher substituted and synthetically challenging octalones, many research groups have investigated alternative methods. Generally, the more problematic step of the Robinson annulation is the intermolecular 1,4-addition and procedures involving a stepwise annulation by1,4-addition and aldol condensation show more promising results.

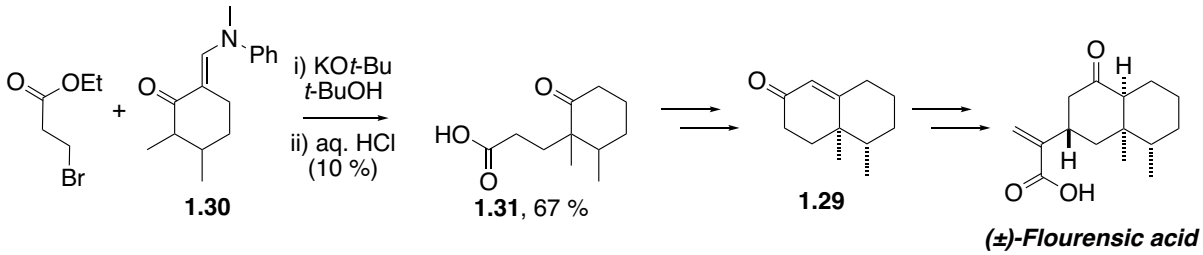
A stepwise annulation procedure was applied in the synthesis of flourensic acid.[59] In order to increase the selectivity of the process, masking of the methylene group in α-position of the carbonyl group of the cyclohexanone was performed. The synthetic route toward octalone **1.29** had already been described before for the total synthesis of racemic fukinone and (+)-hydroxyeremophilone by the group of A. R. Pinder.[17] Initial investigations aiming at the preparation of **1.29** started from 2,3-dimethylphenol, which was converted to a mixture of *cis*- and *trans*-2,3-dimethylcyclohexanone (Scheme 1.18). Robinson annulation with methyl vinyl ketone under various conditions formed only around 15 % of the desired bicyclic compound in an epimeric mixture that could not be fully separated by fractional distillation. Based on studies by Piers and co-workers, who had used the *n*-butylthiomethylene blocking group[60] in the synthesis of aristolone,[61] a methylanilin-substituted enone was applied in the annulation procedure. By thus masking the CH_2 at one of the two α-positions of the cyclohexanone carbonyl group, selective electrophilic 1,4-addition at C5 of **1.30** to the Michael acceptor formed *in situ* from ethyl 3-bromopropionate was possible and gave the desired keto acid **1.31** in 67 % yield after hydrolysis. An aldol condensation furnished the desired octalone **1.29**, which was further reacted to racemic flourensic acid.

H. Faubl, T. M. Warne, *Chem. Commun. (London)* **1967**, 753-754.*Commun. (London)* **1968**, 1152-1154; J. A. Marshall, H. Faubl, T. M. Warne, *Chem. Commun. (London)* **1967**, 753-754.

[59] J. N. Herron, A. R. Pinder, *J. Chem. Soc., Perkin Trans. 1* **1983**, 161-166.

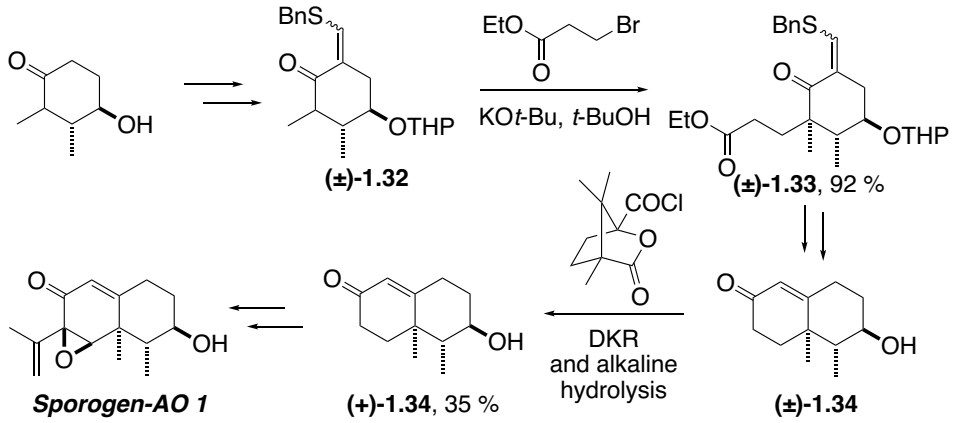
[60] R. E. Ireland, J. A. Marshall, *J. Org. Chem.* **1962**, *27*, 1615-1619.

[61] E. Piers, W. d. Waal, R. W. Britton, *Can. J. Chem.* **1969**, *47*, 4299-4306.



Scheme 1.18: Application of methylene blocking in the synthesis of racemic flourensic acid.

Similarly, masking of one of the CH_2 groups in α-position of 2,3-dimethyl cyclohexanone as the benzylthiomethylene derivative was applied in the first enantioselective synthesis of sporogen-AO 1 by K. Mori and H. Tumara (Scheme 1.19).[62] Addition of masked cyclohexanone **1.32** to the Michael acceptor vinyl ester derived from ethyl-3-bromopropanoate gave keto ester **1.33** in 92 % yield. After octalone (±)-**1.34** had been obtained, dynamic kinetic resolution of the racemic mixture proved difficult with stereo-differentiating reagents as well as with enzymatic methods; only camphanic chloride showed promising results. After separation of the octalone ester diastereomers derived from (±)-**1.34** and hydrolysis of the ester, enantiopure (+)-**1.34** was obtained. Thus, the total synthesis of sporogen-AO 1 was finally achieved in a total of 25 steps starting from 2,3-dimethylhydroquinone.



Scheme 1.19: Enantioselective total synthesis of (+)-sporogen-AO 1 *via* a chiral octalone ester.

1.4.1.2 Modification of Alkylating Reagent

Instead of modification of the cyclohexanone substrate, replacement of the electrophilic alkylating agent was investigated as well. The Wichterle modification,[63] already introduced in 1948, uses masked carbonyl groups as alkylating agents (*e.g.* 1,3-dichloro-*cis*-2-butene) to

[62]K. Mori, H. Tamura, *Liebigs Ann. Chem.* **1988**, 97-105.

[63] O. Wichterle, J. Prochazka, J. Hoffman, *Coll. Czech. Chem. Commun.* **1948**, *3*, 300-315.

avoid polymerization of the Michael adducts. However, additional steps after the 1,4-addition to unmask and to transform the halides to the corresponding ketones makes this approach laborious and less elegant. A more suitable proposal was elaborated by the group of G. Stork, who introduced the Stork silylenone,[64] a vinyl ketone that is α-substituted by a silyl group for stabilization of the adjacent negative charge in order to prevent polymerization. This procedure featuring addition of the electrophile to the lithium enolate, generated from the corresponding cyclohexanone *via* silyl enol ether formation, led to significantly increased yields for various substrates.

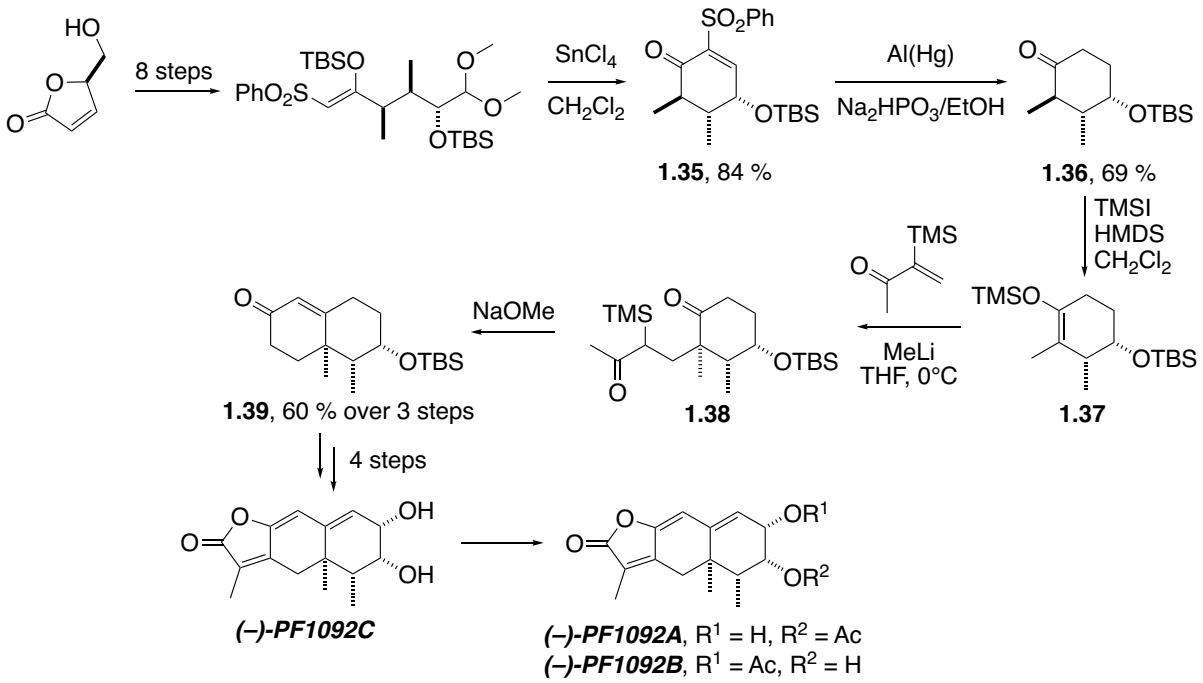
In eremophilane syntheses, the Stork procedure found application in the preparation of the progesterone receptor ligands (–)-PF1092A, B and C (Scheme 1.20).[65] These compounds are eremophilenolides characterized by four contiguous *cis*-substituents in the A-ring.[66] The synthesis starts from commercially available *R*-(+)-5-hydroxymethyl-2(5*H*)-furanone and features an $SnCl_4$-promoted cyclization to construct the substituted cyclohexanone **1.35** in nine steps. Desulfurization of **1.35** with Al(Hg) with concomitant reduction of the double bond set the stage for the stepwise Robinson annulation procedure using Stork silylenone. Silylation of **1.36** gave the corresponding silyl enol ether **1.37**, which was reacted with silylated methyl vinyl ketone to form the diketone **1.38**. Basic conditions then triggered both the aldol condensation and cleavage of the TMS moiety to form octalone **1.39**. (–)-PF1092C was obtained after four steps from octalone **1.39** and selective acetylation procedures gave access to (–)-PF1092A and (–)-PF1092B.[67]

[64] G. Stork, B. Ganem, *J. Am. Chem. Soc.* **1973**, *95*, 6152-6153.

[65] K. Tatsuta, S. Yasuda, K.-i. Kurihara, K. Tanabe, R. Shinei, T. Okonogi, *Tetrahedron Lett.* **1997**, *38*, 1439-1442.

[66] K. Yamakawa, M. Kobayashi, S. Hinata, T. Satoh, *Chem. Pharm. Bull.* **1980**, *28*, 3265-3274.

[67] K. Kurihara, K. Tanabe, R. Shinei, T. Okonogi, Y. Ohtsuka, S. Omoto, S. Yasuda, K. Tatsuta, *J. Antibiot.* **1997**, *50*, 360-362.



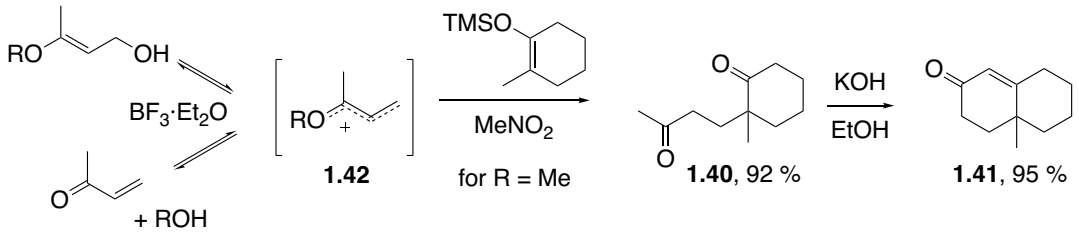
Scheme 1.20: Total synthesis of eremophilenolides (–)-PF1092A, B and C by Stork annulation.

Major drawbacks of Stork's method are the need to prepare the functionalized Michael adducts as well as the removal of the silyl protecting group by harsh reaction conditions after completion of the 1,4-addition.

In addition to the previously described reagents used under basic conditions, the group of P. Duhamel introduced hemiacetal vinylogues as methyl vinyl ketone equivalents, which are reacted in a Lewis acid-mediated Robinson annulation (Scheme 1.21).[68] When the silyl enol ether derived from 2-methylcyclohexanone was subjected to the mildly Lewis acidic reaction conditions, diketone **1.40** was obtained in 92 % yield. Basic conditions then triggered aldol condensation to the octalone **1.41**. In later experiments, it was observed that *in situ* generation of the intermediate carbocation **1.42** from an enone (such as methyl vinyl ketone) and an alcohol or acetic acid gave the same results, thus avoiding the preparation of hemiacetal vinylogues.[69]

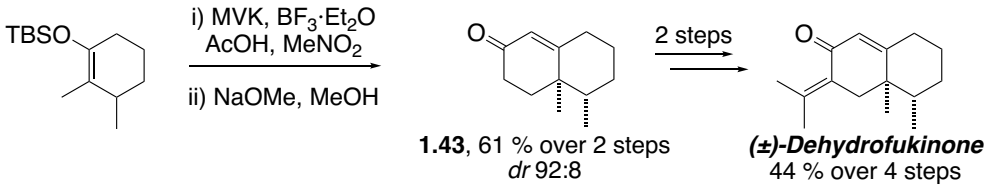
[68] P. Duhamel, J.-M. Poirier, G. Tavel, *Tetrahedron Lett.* **1984**, *25*, 43-46; P. Duhamel, L. Hennequin, N. Poirier, J.-M. Poirier, *Tetrahedron Lett.* **1985**, *26*, 6201-6204; P. Duhamel, L. Hennequin, J. M. Poirier, G. Tavel, C. Vottero, *Tetrahedron* **1986**, *42*, 4777-4786.

[69] P. Duhamel, G. Dujardin, L. Hennequin, J. M. Poirier, *J. Chem. Soc., Perkin Trans. 1* **1992**, 387-396.



Scheme 1.21: Formation of the intermediate carbocation by reaction with a Lewis acid from either hemiacetal vinylogues or from methyl vinyl ketone in a protic solvent; and annulation reaction of intermediate carbocation with a silyl enol ether.

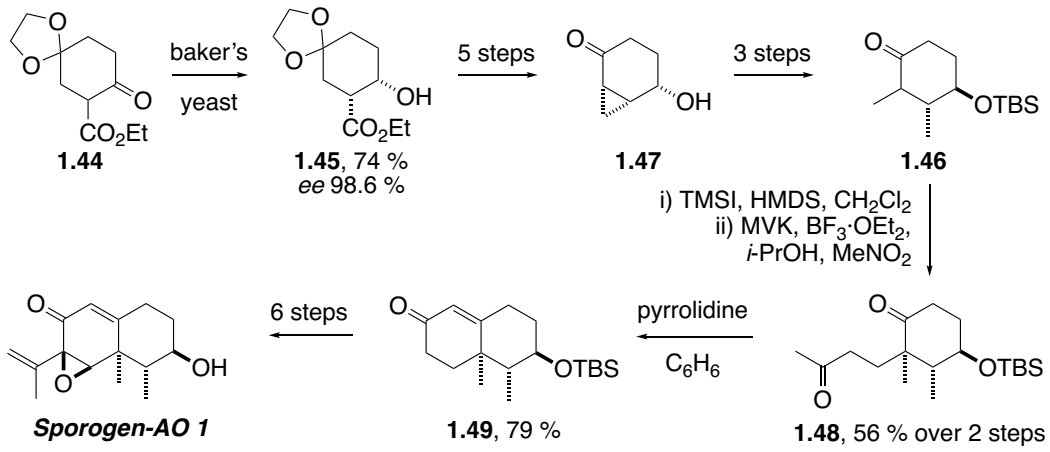
This elegant and very efficient approach in terms of yield and stereoselectivity was applied in several eremophilane syntheses. Starting from the silyl enol ether derived from 2,3-dimethylcyclohexanone, P. Duhamel synthesized octalone **1.43** in 61 % yield and with a diastereomeric ratio of 92:8 in favor of the product with a *cis*-orientation of the methyl groups at C4 and C5. After introduction of the side chain, (±)-dehydrofukinone was obtained in 44 % yield over four steps (Scheme 1.22).[69]



Scheme 1.22: Concise route to (±)-dehydrofukinone.

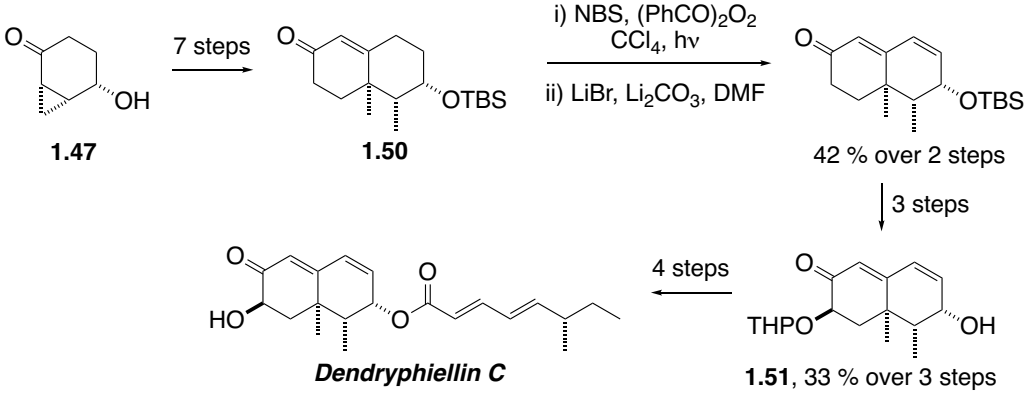
In the same year as the primary synthesis of (+)-sporogen-AO 1 was reported, the group of T. Kitahara presented an optimized approach toward the same target molecule featuring an early enzymatic resolution and the application of Duhamel's annulation procedure.[70] Reduction of β-ketoester **1.44** by baker's yeast gave the hydroxyester **1.45** with an *ee* of 98.6 %, which was converted to dimethylated cyclohexanone **1.46** in eight steps *via* cyclopropane **1.47** (Scheme 1.23). The presence of the cyclopropane ring was found to be essential for triggering the formation of the desired isomer in the Mitsunobu inversion reaction. After the corresponding silyl enol ether had been prepared, Lewis acid-mediated alkylation gave the 1,5-diketone **1.48** in 56 % yield over two steps. Aldol condensation was catalyzed by pyrrolidine in benzene and the prepared octalone **1.49** was converted to sporogen-AO 1 in six more steps.

[70] T. Kitahara, H. Kurata, K. Mori, *Tetrahedron* **1988**, *44*, 4339-4349.



Scheme 1.23: Optimized enantioselective total synthesis of (+)-sporogen-AO 1.

In a similar manner without inversion at C3 of **1.47**, trinor-eremophilane dendryphiellin C was synthesized from the same cyclopropane intermediate (Scheme 1.24).[71] After octalone **1.50** had been obtained, C1=C2 unsaturation was introduced by radical bromination followed by dehydrobromination using LiBr and Li_2CO_3. Oxygenation using Davis' *N*-sulfuryloxaziridine and protecting group modifications gave α-keto ether **1.51** in moderate yield. Installation of the aliphatic side chain finally led to dendryphiellin C.



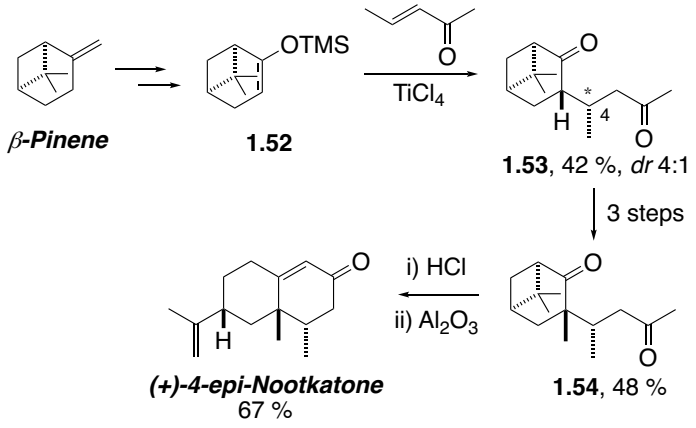
Scheme 1.24: Total synthesis of dendryphiellin C starting from cyclopropane intermediate **1.47**.

Diastereoselective pathways by annulation of precursors derived from the chiral pool are extensively applied in the preparation of enantiopure natural products. R. Robinson and coworkers described the annulation of dihydrocarvone for the syntheses of cyperones already in 1937.[72] In 1980, the group of A. Yoshikoshi presented a stereoselective synthesis of (+)-4-*epi*-nootkatone starting from β-pinene (Scheme 1.25).[73]

[71] H. Akao, H. Kiyota, T. Nakajima, T. Kitahara, *Tetrahedron* **1999**, *55*, 7757-7770.

[72] P. S. Adamson, F. C. McQuillin, R. Robinson, J. L. Simonsen, *J. Chem. Soc.* **1937**, 1576-1581.

[73] T. Yanami, M. Miyashita, A. Yoshikoshi, *J. Org. Chem.* **1980**, *45*, 607-612.



Scheme 1.25: Synthesis of (+)-4-*epi*-nootkatone from β-pinene.

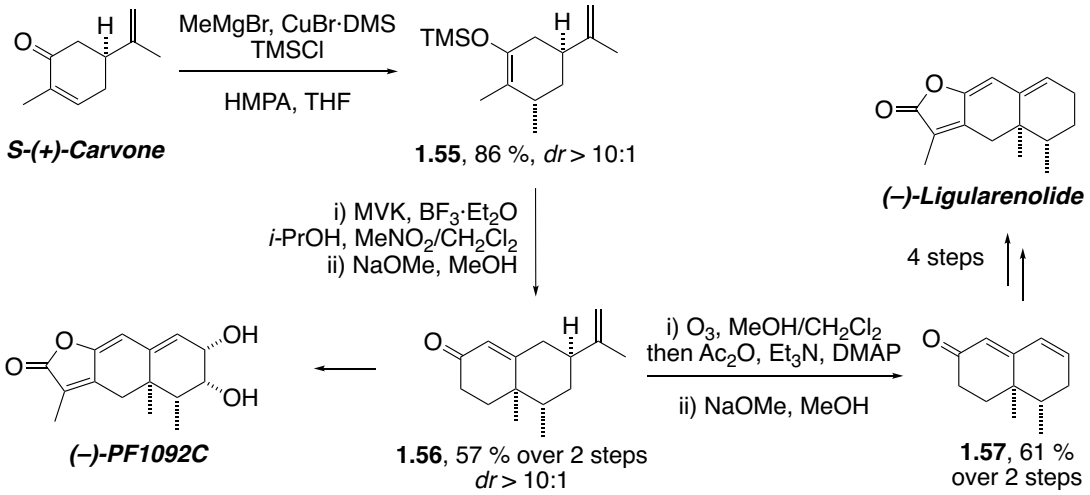
Oxidative cleavage and silyl ether formation yields silyl enol ether **1.52**. Lewis acid-mediated Michael addition to *trans*-3-penten-2-one gives the diketone **1.53**. Unfortunately, the desired isomer for the preparation of (+)-nootkatone was the minor one formed in this reaction (*dr* 1:4), and therefore the synthesis of (+)-4-*epi*-nootkatone was presented. The inseparable 4:1 diastereomeric mixture of **1.53** was subjected to stereoselective methylation, and annulation as well as cleavage of the cyclobutane ring of **1.54** was triggered by treatment with anhydrous hydrochloric acid. Dehydration using activated aluminum oxide afforded (+)-4-*epi*-nootkatone in 67 % yield over two steps.

The group of A. de Groot applied Lewis acid-mediated Michael addition for the preparation of (–)-PF1092C and (–)-ligularenolide starting from *S*-carvone (Scheme 1.26).[74] Conjugate addition for the installation of a carbon substituent at C4 to form **1.55** was followed by a two-step Robinson annulation procedure.[75] The isopropenyl group of **1.56**, which served as a removable directing group for stereoselective synthesis, was then removed by a Criegee rearrangement,[76] and the obtained dienone **1.57** transformed to (–)-ligularenolide in four steps. Alternatively, octalone **1.56** was converted to (–)-PF1092C in five steps featuring cleavage of the isopropenyl group, isomerization and lactone moiety installation.

[74] L. H. D. Jenniskens, A. de Groot, *Tetrahedron Lett.* **1997**, *38*, 7463-7464; L. H. D. Jenniskens, A. de Groot, *Tetrahedron* **1998**, *54*, 5617-5622.

[75] A. A. Verstegen-Haaksma, H. J. Swarts, B. J. M. Jansen, A. de Groot, *Tetrahedron* **1994**, *50*, 10073-10082.

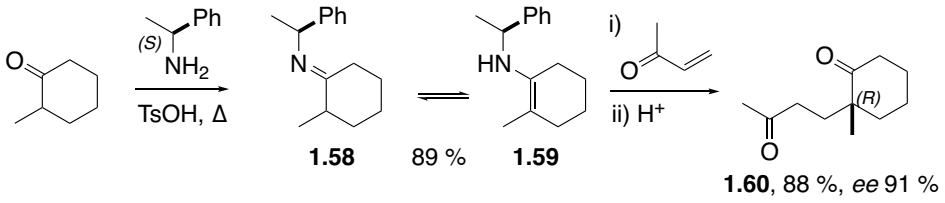
[76] R. Criegee, *Angew. Chem. Int. Ed.* **1975**, *14*, 745-752; R. Criegee, W. Schnorrenberg, *Liebigs Ann. Chem.* **1948**, *560*, 141-148.



Scheme 1.26: Total synthesis of (–)-PF1092C and (–)-ligularenolide from *S*-carvone involving a Lewis acid-mediated Robinson annulation.

1.4.1.3 Chiral Imines as Robinson Annulation Precursors (Pfau-d'Angelo method)

In 1985, Pfau *et al.* published the first asymmetric Michael addition under neutral conditions using chiral imines.[77] Condensation of racemic 2-methylcyclohexanone with readily available *S*- or *R*-1-pheynlethylamine forms a chiral imine **1.58**, which is in equilibrium with its enamine tautomer **1.59**. Reaction with methyl vinyl ketone gives the diketone **1.60** in high yield and enantiomeric excess (Scheme 1.27). This versatile method with a broadly expanded scope found considerable attention in the synthetic community, and has already been extensively reviewed.[78,55]



Scheme 1.27: Pfau-d'Angelo method for enantioselective 1,4-addition reaction.

In 1997, the group of H. J. Bestmann reported the first enantioselective total synthesis of (+)-petasin and its isomer (+)-isopetasin using the Pfau-d'Angelo approach.[79] However, chirality was not introduced by 1,4-addition, but by enzymatic kinetic resolution using lipase of *Candida cylandrea* (Scheme 1.28). Protecting group modification, oxidation and installation of the methyl substituents at C4 and C5 of **1.61** set the stage for the annulation reaction.

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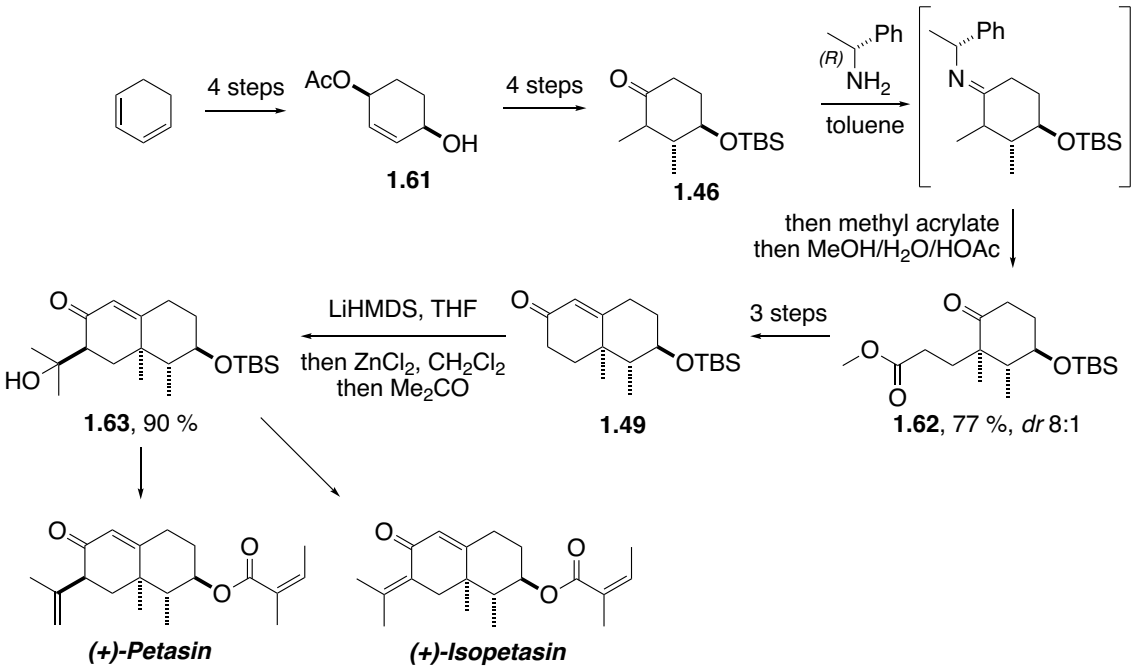
[77] M. Pfau, G. Revial, A. Guingant, J. d'Angelo, *J. Am. Chem. Soc.* **1985**, *107*, 273-274.

[78] J. d'Angelo, D. Desmaële, F. Dumas, A. Guingant, *Tetrahedron: Asymmetry* **1992**, *3*, 459-505.

[79] M. C. Witschel, H. J. Bestmann, *Synthesis* **1997**, *1997*, 107-112.

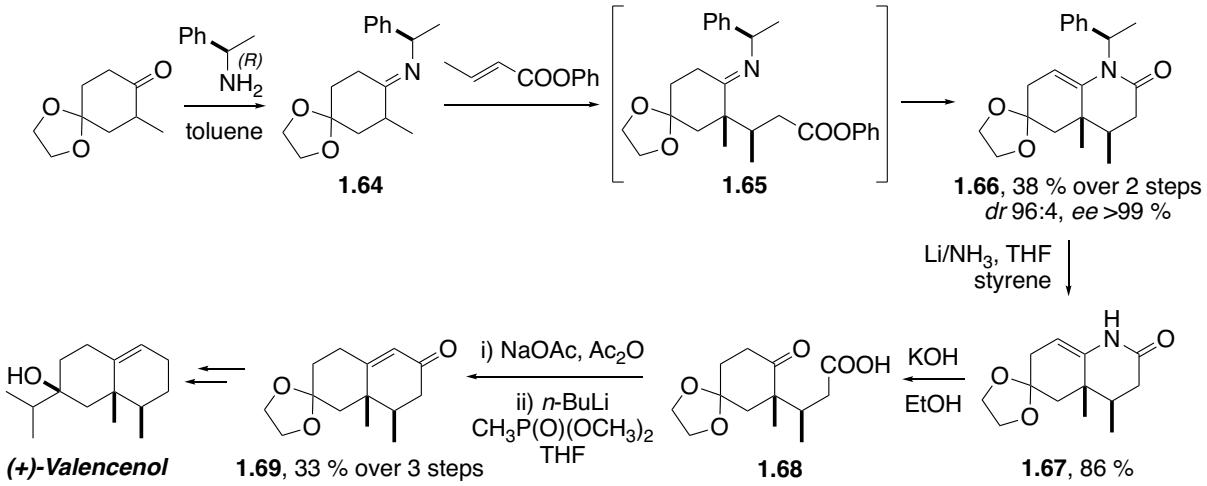


Scheme 1.28: Total synthesis of (+)-petasin and (+)-isopetasin using the Pfau-d'Angelo method on a chiral cyclohexanone precursor.

While chiral imines derived from achiral cyclohexanones react with high diastereoselectivity in the alkylation reaction, this is not the case with substituted chiral cyclohexanone precursors. However, a matched situation was achieved by using *R*-1-phenylethylamine in the reaction of 2,3-dimethylated cyclohexanone **1.46** with methyl acrylate to obtain the keto ester **1.62** in 77 % yield and a *dr* of 8:1 after *in situ* hydrolysis of the imine. A three-step procedure formed the octalone **1.49**, whose lithium enolate reacted with acetone in an aldol addition, thus forming the C7-alkylated octalone **1.63** as a single diastereoisomer. Mesylation and elimination of the tertiary alcohol, followed by silyl deprotection and coupling to a mixed anhydride of angelic acid yielded (+)-isopetasin. The isomer (+)-petasin was obtained by installation of the ester at C7, followed by selective elimination using triflic anhydride and Hünig's base.

In a formal synthesis of (+)-valencenol, M. Pfau and coworkers presented the enantioselective Michael addition of a chiral imine derived from 4-protected 2-methyl-cyclohexane-1,4-dione to phenyl crotonate (Scheme 1.29).[80]

[80] G. Revial, I. Jabin, M. Redolfi, M. Pfau, *Tetrahedron: Asymmetry* **2001**, *12*, 1683-1688.



Scheme 1.29: Total synthesis of (+)-valencenol using the Pfau-d'Angelo method to install the stereogenic centers at C4 and C5.

Initial experiments revealed that *trans*-3-penten-2-one did not react with imines derived from 2-methylcyclohexanone at room temperature and polymerized at 60°C. Nevertheless, after imine **1.64** had been formed, reaction with phenyl crotonate gave the Michael adduct **1.65**, which spontaneously cyclized to the lactam **1.66** under the given reaction conditions in 38 % overall yield and excellent diastereo- and enantioselectivity. In addition to the usually formed quaternary stereogenic center, a tertiary one was created in the 1,4-addition reaction. After C_1 homologation of lactam **1.66** had failed, a Belleau-Fujimoto reaction proved to be successful. Reductive cleavage of **1.66** formed lactam **1.67**, which gave keto acid **1.68** after hydrolysis and octalone **1.69** after subsequent C_1 homologation. Upon reduction of the C2-carbonyl group and deprotection at C7, Grignard reaction[81] of the obtained ketone with isopropylmagnesium bromide gave (+)-valencenol.

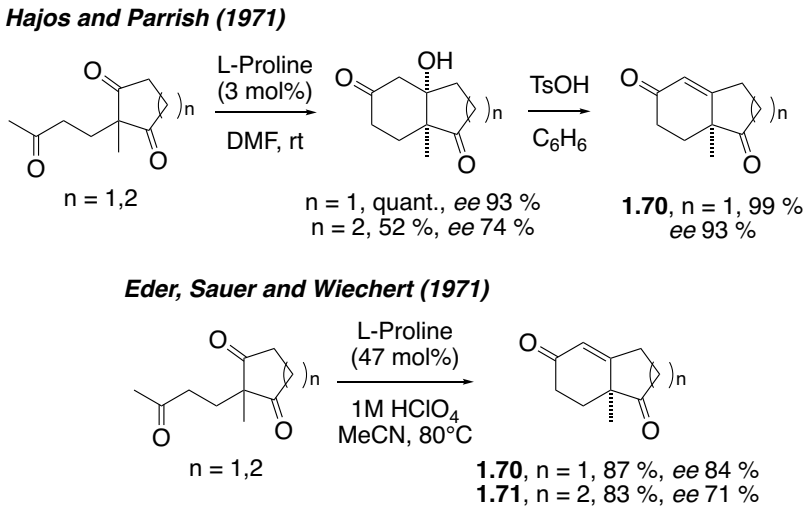
1.4.1.4 Enantioselective 1,3-Diketone Robinson Annulation – Syntheses Starting from Wieland-Miescher Ketones

Due to the weak acidity of α-hydrogen atoms of monoketones ($pK_a \approx 20–25$), the Robinson annulation procedure usually requires strong bases. To enable this reaction under milder conditions, the use of 1,3-dicarbonyl compounds is highly desirable, thus reducing the amount of side product formation, polyalkylation at the α-positions of ketones and/or polymerization of the electrophiles. In the early 1970s, Z. G. Hajos and D. R. Parrish at Hoffmann La Roche,[82]

[81] M. Tori, N. Tsuyama, K. Nakashima, M. Sono, Y. Asakawa, *J. Chem. Res. (S)* **1990**, 164-165.

[82] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615-1621; Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1612-1615.

as well as U. Eder, G. Sauer and R. Wiechert at Schering AG[83] reported on proline-catalyzed enantioselective syntheses of bicyclic diketones (Scheme 1.30). This asymmetric intramolecular aldol reaction was mainly pioneered for the construction of steroidal CD-rings and is well-known today as the Hajos-Parrish-Eder-Sauer-Wiechert transformation.



Scheme 1.30: Asymmetric aldol reaction for the construction of bicyclic diketones as decribed by Z. G. Hajos and D. R. Parrish, as well as U. Eder, G. Sauer and R. Wiechert (**1.70**, n = 1: Hajos-Parrish-Eder-Sauer-Wiechert ketone; **1.71**, n = 2: Wieland-Miescher ketone).

Since its discovery, many optimized protocols have been reported and the method was extended to numerous other reactions, including Michael additions,[84] Mannich reactions[85] and α-alkylations[86] or α-aminations[87] of ketones. With regard to the former, T. Bui and C. F. Barbas III reported that proline can catalyze the 1,4-addition as well as the aldol condensation step in a one-pot Robinson annulation.[88] Though a very efficient reaction for synthesizing bicyclic diketones, this method is only rarely applied in eremophilane synthesis. This can be explained by the additional steps required for the installation of a carbon residue next to the angular methyl group in Wieland-Miescher ketone (WMK) to form the characteristic vicinal dimethyl-motif in eremophilanes.

[83] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, *10*, 496-497.

[84] B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423-2425.

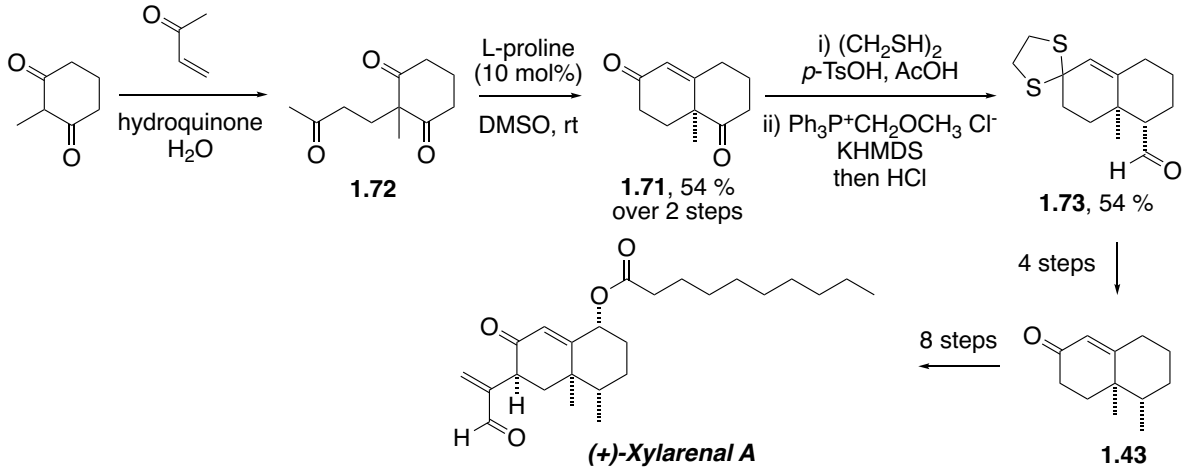
[85] B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827-833.

[86] N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450-451.

[87] A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 1790-1793.

[88] T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951-6954.

In 2005, J. Bonjoch and coworkers reported the enantioselective synthesis of (+)-xylarenal A, the first totally synthetic eremophilane bearing a vinyl aldehyde side chain at C7, starting from optically active WMK (Scheme 1.31).[89] This bicycle was prepared according to the method described by N. Harada *et al.*:[90] a simplified protocol for the 1,4-addition gave diketone intermediate **1.72**, which was stirred at room temperature in the presence of L-proline in degassed DMSO for six days. WMK (**1.71**) was obtained in 82 % yield with 69 % *ee*, and the desired enantiomer was enriched by several crystallization steps. The chemical modifications necessary to install the one-carbon unit at C4 were reported by L. A. Paquette *et al.* in the total synthesis of the diterpene lactone (+)-cleomeolide:[91] after dithioketalization of the C8-carbonyl group, C1 homologation using *in situ* prepared (methoxymethylene)triphenylphosphorane and acidic hydrolysis formed the aldehyde **1.73**. A three-step protocol then formed the octalone **1.43**, which was subjected to γ-oxygenation at C1, installation of the side chain at C7, and esterification to install the aliphatic residue to give (+)-xylanrenal A.



Scheme 1.31: Enantioselective total synthesis of (+)-xylarenal A starting from chiral Wieland-Miescher ketone.

In order to determine the absolute stereochemistry and to gain access to derivatives for SAR studies, the total synthesis of integric acid starting from aldehyde intermediate **1.73** was investigated.[92] Integric acid was first isolated from the fermentation broth of *Xylaria* sp. and showed inhibition of HIV-1 integrase, a key enzyme created by the retrovirus to enable

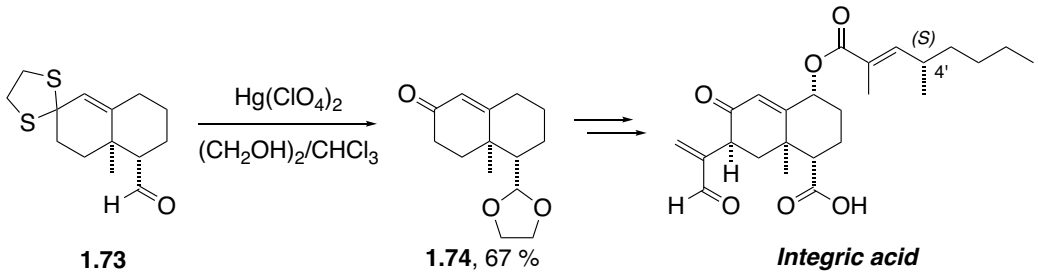
[89] S. Díaz, A. González, B. Bradshaw, J. Cuesta, J. Bonjoch, *J. Org. Chem.* **2005**, *70*, 3749-3752.

[90] N. Harada, T. Sugioka, H. Uda, T. Kuriki, *Synthesis* **1990**, 53-56.

[91] L. A. Paquette, T.-Z. Wang, C. M. G. Philippo, S. Wang, *J. Am. Chem. Soc.* **1994**, *116*, 3367-3374.

[92] D. C. J. Waalboer, H. A. van Kalkeren, M. C. Schaapman, F. L. van Delft, F. P. J. T. Rutjes, *J. Org. Chem.* **2009**, *74*, 8878-8881.

integration of its genetic material into the DNA of an infected cell.[93] A one-step orthogonal deprotection/protection step of aldehyde **1.73** formed octalone **1.74** and already set the stage for γ-oxygenation and installation of the side chains at C7 and C1–OH to form integric acid and its C4'-diastereoisomer (Scheme 1.32). This led to the assignment of an *S*-C4'-configuration for natural integric acid.



1.73 **1.74**, 67 % ***Integric acid***

Scheme 1.32: Enantioselective total synthesis of integric acid inspired by the synthesis of (+)-xylarenal A.

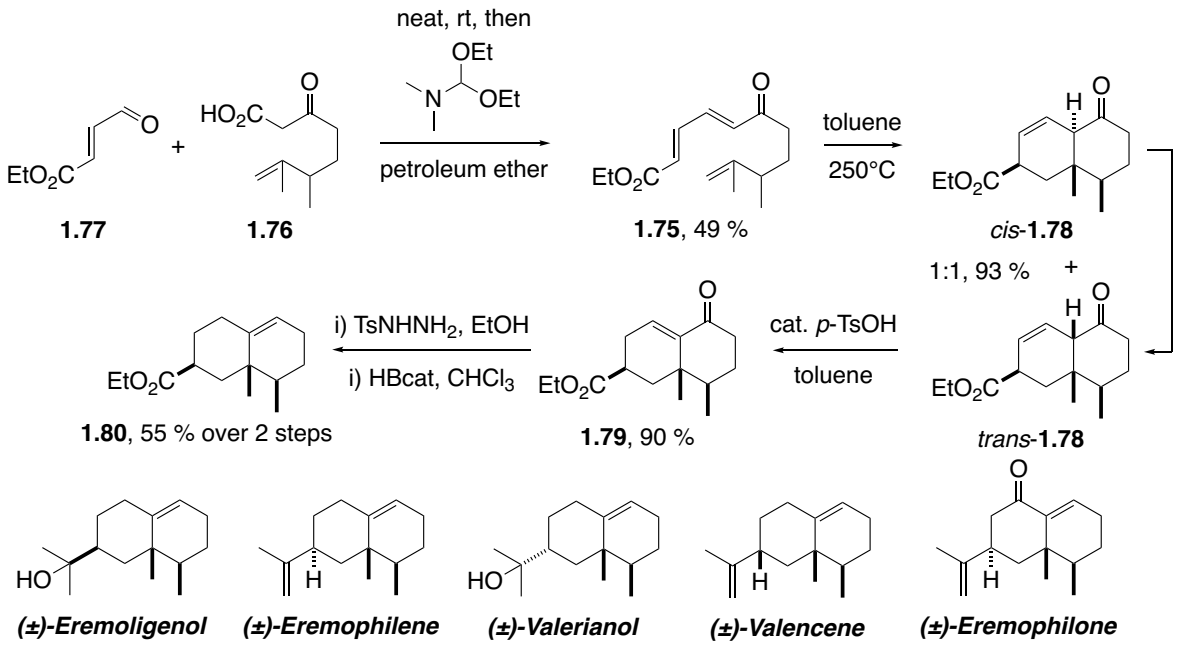
1.4.2 Diels-Alder Procedures

1.4.2.1 Intramolecular Diels-Alder Approach

An intramolecular Diels-Alder approach for the construction of eudesmane and valencane sesquiterpenes was presented by F. Näf *et al*.[94] The acyclic triene precursor **1.75** was prepared by a decarboxylative Knoevenagel condensation of the β-keto acid **1.76** and conjugated aldehyde **1.77** (Scheme 1.33). Heating of this Diels-Alder precursor in toluene at 250°C formed, depending on the purity of **1.75**, either a 1:1 mixture of the bicyclic decalins *cis*-**1.78** and *trans*-**1.78** in 93 %, or only the more stable *cis*-isomer. Acid-catalyzed isomerization gave α,β-unsaturated enone **1.79**, which was converted to **1.80** by heating the tosylhydrazone derivative of **1.79**, before mild hydride reduction using catecholborane. Ester **1.80** served as a key intermediate for the racemic preparation of eremoligenol, eremophilene, valerianol, valencene and eremophilone.

[93] S. B. Singh, D. Zink, J. Polishook, D. Valentino, A. Shafiee, K. Silverman, P. Felock, A. Teran, D. Vilella, D. J. Hazuda, R. B. Lingham, *Tetrahedron Lett.* **1999**, *40*, 8775-8779.

[94] F. Näf, R. Decorzant, W. Thommen, *Helv. Chim. Acta* **1982**, *65*, 2212-2223; F. Näf, R. Decorzant, W. Thommen, *Helv. Chim. Acta* **1979**, *62*, 114-118.



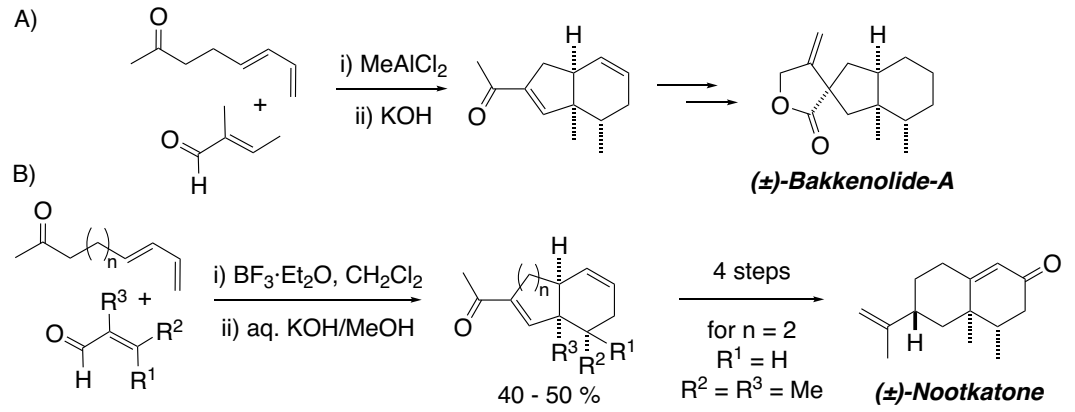
Scheme 1.33: Intramolecular Diels-Alder reaction for the divergent preparation of eremophilane-type sesquiterpenes.

1.4.2.2 Intermolecular Diels-Alder Approach

In 2004, the group of D. S. Reddy introduced a stereocontrolled intermolecular Diels-Alder/aldol approach to construct the *cis*-hydrindane motif in the total synthesis of bakkenolide-A (Scheme 1.34, A).[95] Bakkenolide-A is a member of the bakkane family, which is proposed to be biogenetically derived from eremophilane precursors. The same procedure was extended to the preparation of *cis*-decalones and by varying the substituents at the dienophile, several new members featuring *cis*-hydrindane and *cis*-decalone systems were accessible, out of which one derivative was converted to racemic nootkatone (Scheme 1.34, B).[96]

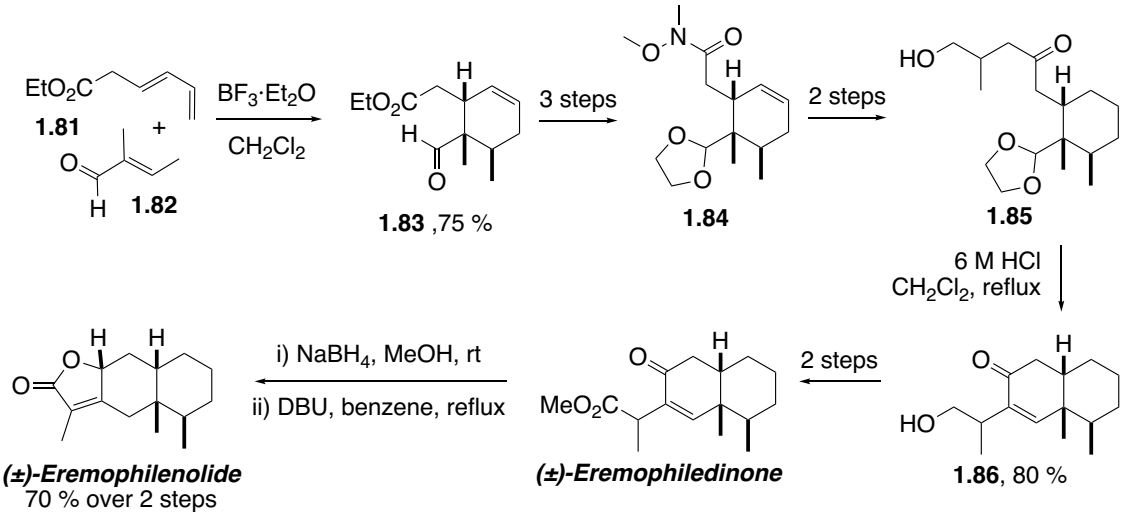
[95] D. S. Reddy, *Org. Lett.* **2004**, *6*, 3345-3347.

[96] K. L. Handore, B. Seetharamsingh, D. S. Reddy, *J. Org. Chem.* **2013**, *78*, 8149-8154.



Scheme 1.34: Intermolecular Diels-Alder reaction in the racemic synthesis of bakkenolide-A.

In the meantime, D. S. Reddy and coworkers also applied their approach for the synthesis of several eremophilanes. In their first report, substituted A-rings for racemic syntheses of eremophilenolide, eremophiledinone and deoxyeremopetasidione have been presented (Scheme 1.35).[97]



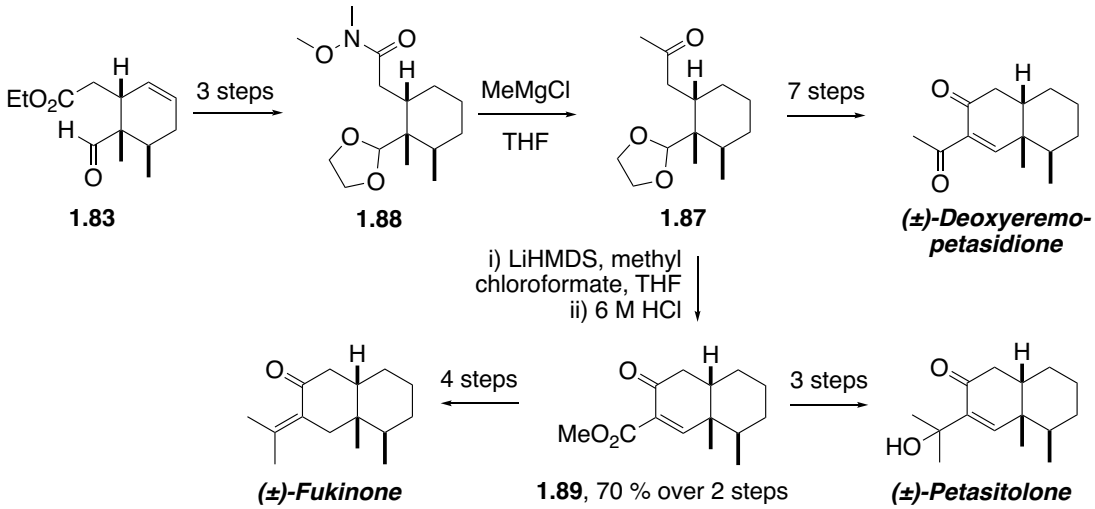
Scheme 1.35: Total synthesis of (±)-eremophiledinone and (±)-eremophilenolide.

The synthesis commenced with diene **1.81** and tiglic aldehyde **1.82**, which formed the desired Diels-Alder adduct **1.83** with high diastereoselectivity upon treatment with the Lewis acid $BF_3 \cdot OEt_2$. After protection of the aldehyde, the ester moiety was modified to form Weinreb amide **1.84**. A Grignard reaction and hydrogenation of the C1=C2 double bond furnished the primary alcohol **1.85**, from which the B-ring was constructed by an aldol condensation reaction

[97] P. Srinivas, D. S. Reddy, K. S. Kumar, P. K. Dubey, J. Iqbal, P. Das, *Tetrahedron Lett.* **2008**, *49*, 6084-6086.

to give the 6/6 bicyclic system **1.86**. Oxidation and esterification yielded (±)-eremophiledinone, which was converted to (±)-eremophilenolide in two steps.

The group of D. S. Reddy further used Diels-Alder adduct **1.83** in the synthesis of (±)-deoxyeremopetasidione,[97] (±)-fukinone and (±)-petasitolone[98] *via* methyl ketone **1.87** as common intermediate (Scheme 1.36). The saturated Weinreb amide **1.88** was synthesized in a similar manner as shown in the previous synthesis for **1.84**, and Grignard reaction of **1.88** with MeMgCl gave the key intermediate **1.87**. After carbon chain elongation and treatment with acid, intramolecular aldol condensation gave **1.89**. From this octalone, the synthesis of (±)-petasitolone was achieved in three and of (±)-fukinone in four steps.



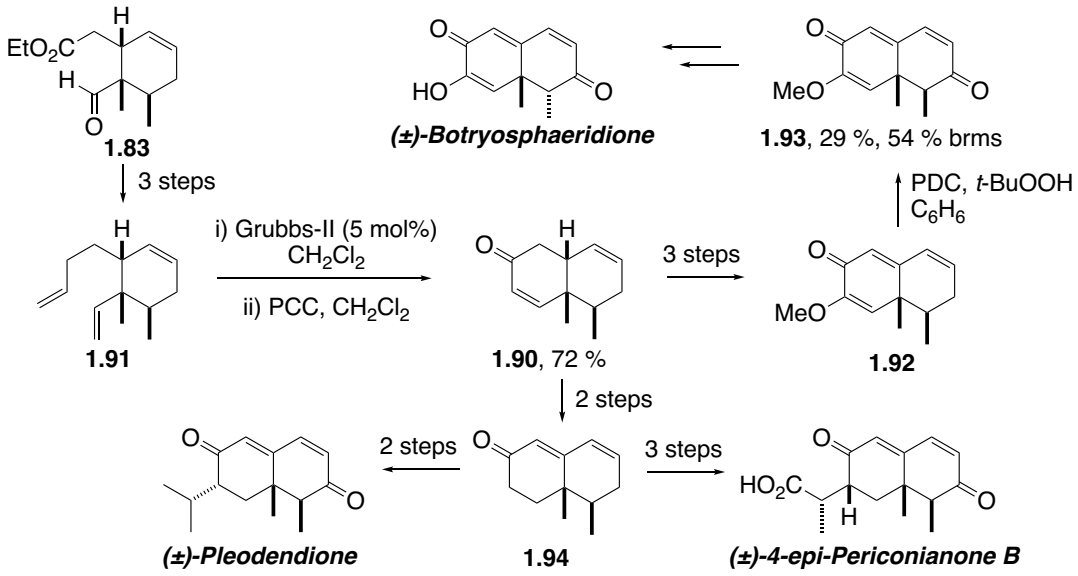
Scheme 1.36: Total synthesis of (±)-deoxyeremopetasidione, (±)-fukinone and (±)-petasitolone.

Very recently, another divergent approach towards synthetic (±)-botryosphaeridione, (±)-pleodendione and (±)-4-*epi*-periconianone B has been published.[99] To this end, the synthesis to the common octalone intermediate **1.90** commenced from Diels-Alder adduct **1.83**, which was submitted to Wittig olefination of the aldehyde, reduction of the ester and Grignard addition of vinylmagnesium bromide to form the triene **1.91** (Scheme 1.37). Ring closing metathesis using Grubbs 2nd generation catalyst and oxidation by pyridinium chlorochromate gave the desired *cis*-octalone **1.90**. Several oxidative modifications led to diosphenol **1.92**, which was shown to react sluggishly in the subsequent allylic oxidation step to **1.93**. Nevertheless, (±)-botryosphaeridione was finally obtained after isomerization at C4 under basic conditions and deprotection of the methyl ether. (±)-Pleodendione and (±)-4-*epi*-periconianone B were accessible *via* the intermediate dienone **1.94**, obtained from octalone **1.90** by a

[98] S. Pasikanti, D. S. Reddy, J. Iqbal, P. K. Dubey, P. Das, *Synthesis* **2009**, 3833-3837.

[99] K. L. Handore, P. D. Jadhav, B. Hazra, A. Basu, D. S. Reddy, *ACS Med. Chem. Lett.* **2015**, *6*, 1117-1121.

reduction/oxidation procedure. Epimerization as for addressing (±)-botryosphaeridione did not take place at either C4 or C11 of 4-*epi*-periconianone B and thus the diastereoisomer periconianone B was not obtained. However, NMR experiments as well as the single crystal X-ray structure of a precursor hinted at the wrong assignment of periconianone B with respect to the stereogenic center at C11 as reported in literature.[100]



Scheme 1.37: Total synthesis of (±)-pleodendione, (±)-botryosphaeridione and (±)-4-*epi*-periconianone B.

1.4.3 Miscellaneous Approaches

As a comprehensive review on the plethora of synthetic approaches towards the more than 1500 members of the eremophilane family of natural products would exceed the scope of this thesis, we will now shortly summarize some of the other routes apart from Diels-Alder strategies and Robinson annulation reactions applied for the construction of eremophilanes. Especially noteworthy are two excellent examples: the eight-step synthesis of (+)-nootkatone by an anionic oxy-Cope reaction in an overall yield of 33 %[101] and the efficient synthesis of ishwarane by a C–H insertion approach.[102]

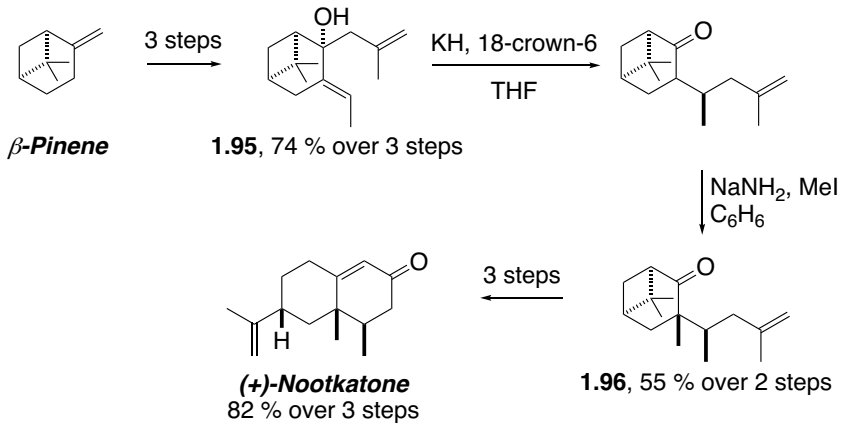
In section 1.4.1.2, Yoshikoshi's synthesis of (+)-4-*epi*-nootkatone starting from β-pinene has been presented. The stereoselective step, Lewis acid-mediated conjugate addition of allyltrimethylsilane to the enone, did not provide the desired isomer so that the synthesis finally yielded (+)-4-*epi*-nootkatone instead of the desired (+)-nootkatone. In 2009, the group of R. A.

[100] D. Zhang, H. Ge, J.-h. Zou, X. Tao, R. Chen, J. Dai, *Org. Lett.* **2014**, *16*, 1410-1413.

[101] A. M. Sauer, W. E. Crowe, G. Henderson, R. A. Laine, *Org. Lett.* **2009**, *11*, 3530-3533.

[102] R. M. Cory, F. R. McLaren, *J. Chem. Soc., Chem. Commun.* **1977**, 587-588.

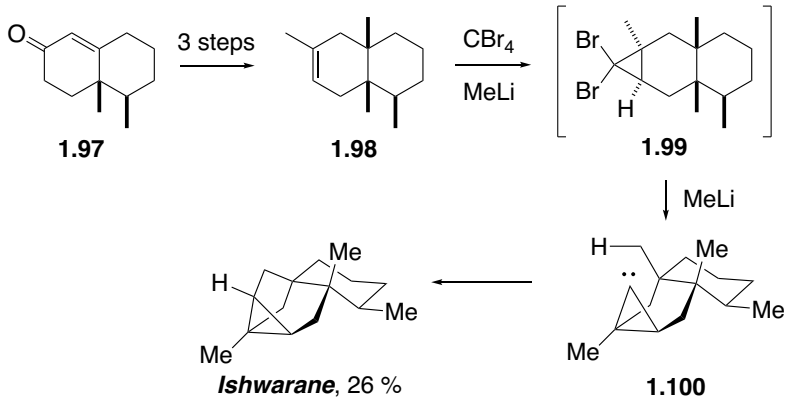
Laine elaborated a different approach toward (+)-nootkatone starting from β-pinene and based on Yoshikoshi's work. A three-step protocol involving oxidative cleavage by inexpensive $KMnO_4$, aldol condensation with acetaldehyde, and stereoselective Grignard addition converted β-pinene to allylated compound **1.95**. An anionic oxy-Cope reaction accounted for the desired configuration at C4, and subsequent stereoselective methylation gave the desired C4/C5 *cis*-dimethylated compound **1.96**. Oxidative cleavage, cyclobutane cleavage and aldol cyclization yielded (+)-nootkatone in a high overall yield of 33 % (Scheme 1.38).



Scheme 1.38: Total synthesis of (+)-nootkatone featuring an anionic oxy-Cope reaction.

Ishwarane is a tetracyclic eremophilane hydrocarbon, characterized by fusion of the isopropenyl carbon atoms C11 and C12 with the decalin core at C7, C8 and C10. In 1977, R. M. Cory and F. R. McLaren reported a "carbon atom insertion" tactic to construct the complex fused skeleton.[102] This very elegant approach was an early demonstration of how easy carbenes can insert into unactivated C–H bonds, and is one of the most impressive applications of C–H activation in total synthesis.[103] Their synthetic protocol started from octalone **1.97**, which was subjected to 1,4-addition of methyl Gilman cuprate to install the methyl group at C10, methyl Grignard addition to the carbonyl group and dehydration of the formed tertiary alcohol (Scheme 1.39). The obtained olefin **1.98** was treated with *in situ* generated dibromocarbene (CBr_4 and MeLi at –78°C) to mediate diastereoselective cyclopropanation to form intermediate **1.99**, which upon warming to –35°C can undergo a lithium-halogen exchange. Subsequent α-elimination then forms cyclopropylcarbene **1.100**, which inserts into the most accessible C–H bond to form ishwarane in 26 % yield.

[103] W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976-1991.



Scheme 1.39: C–H insertion approach for the total synthesis of ishwarane.

1.5 Aim of this Thesis

With these synthetic approaches toward eremophilane natural products in mind, we started to investigate a concise, stereoselective and divergent approach for the preparation of higher oxidized, functionalized and unusually connected members of the eremophilane sesquiterpenes. A major challenge in the constructions of polycyclic scaffolds in terpene natural product synthesis is the investigation of chemical reactions that can compete with the efficiency of natural cyclase enzymes.[104] While the early biosynthetic pathways of carbon skeleton rearrangements are well investigated, C–C bond formation at the later stage of oxidized members of the synthesis, known as tailoring steps, still remains to be discovered. The following chapters deal with the investigation of newly discovered bioactive eremophilanes, with the elaboration of total syntheses for six members of the eremophilane family of natural products as well as with biogenetic hypotheses proposed on the basis of our synthetic studies.

[104]M. Willot, M. Christmann, *Nat. Chem.* **2010**, *2*, 519.

2 TOTAL SYNTHESIS OF PERICONIANONE A

2.1 Introduction

In 2014, J. Dai and co-workers reported on the isolation of the secondary metabolite periconianone A (**2.1**) by bioassay-guided fractionation of the EtOAc extracts from the fermentation broth of *Periconia* sp. F-31, an endophytic fungus obtained from the plant *Annona muricata*.[100] Extensive application of analytical methods such as NMR spectroscopy, ECD calculations, and single crystal X-ray analysis culminated in the structural elucidation of periconianone A, an architecturally complex, rigid, and highly oxidized eremophilane sesquiterpenoid that is built up on a unique 6/6/6 tricarbocyclic skeleton (Figure 2.1). All ring carbon atoms except for one are either stereogenic or sp^2-hybridized; together with five contiguous stereocenters including two adjacent quaternary stereogenic carbon atoms, this structural peculiarity presents an exciting synthetic challenge.

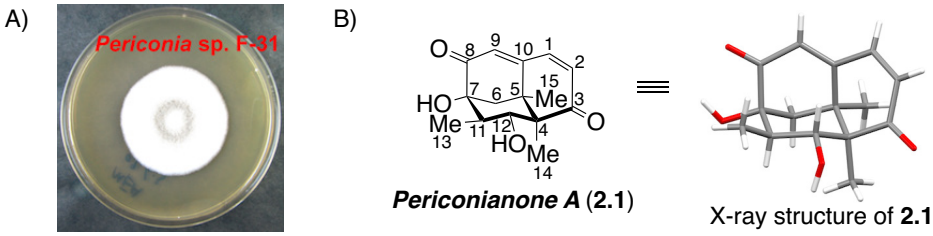


Figure 2.1: A) Culture of endophytic fungus *Periconia* sp. F-31; B) Chemical structure and single crystal X-ray structure of periconianone A (**2.1**).

In addition to its striking structural features, periconianone A displays significant neural anti-inflammatory activity, inhibiting the lipopolysaccharide-induced nitric oxide (NO) production in mouse microglia BV2 cells. The inflammatory mediator NO, one of the key signaling molecules in the human body, is produced by macrophages of the central nervous system, which are controlled by lipopolysaccharide (LPS) activators. There is evidence that the excessive and continuous over production of NO by activated microglia contributes to inflammatory-mediated neurodegeneration and neuronal loss.[105] In addition, reactive microglia might also be jointly responsible for the poor recovery of damaged axons by NO-induced down-regulation of neurite outgrowth.[106] Therefore, manipulation and in particular inhibition of LPS-induced microglial NO production might be a promising strategy to identify effective

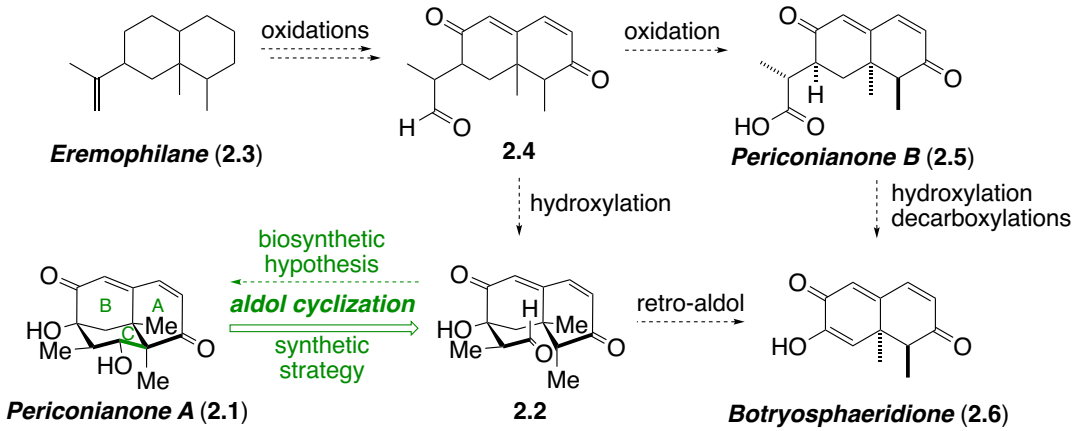
[105] M. L. Block, L. Zecca, J.-S. Hong, *Nat. Rev. Neurosci.* **2007**, *8*, 57.

[106] H. Scheiblich, G. Bicker, *Dev. Neurobiol.* **2015**, *76*, 566-584.

candidates for the treatment of central nervous system inflammation and to aid the recovery and reconstruction of neuronal networks.

2.1.1 Proposed Biosynthesis of Periconianone A

Structural diversity in terpene biosynthesis is usually achieved at the initial cyclase phase by both polyene cyclizations and cationic rearrangements.[107] In contrast, the unprecedented tricarbocyclic cage-like skeleton of periconianone A (**2.1**) is biosynthetically proposed to be the result of an unusual late-stage aldol cyclization of the highly oxidized bicyclic eremophilane precursor **2.2** (Scheme 2.1).[100] Such a C4–C12 linkage forming the additional C-ring in periconianone A is to our knowledge unprecedented in other sesquiterpenoids and its construction involves formation of a motif with two contiguous all-carbon quaternary stereocenters, a challenging structural feature in organic synthesis.[108]



Scheme 2.1: Proposed biosynthetic pathway of periconianone A (**2.1**) and synthetic strategy for the construction of the C-ring.

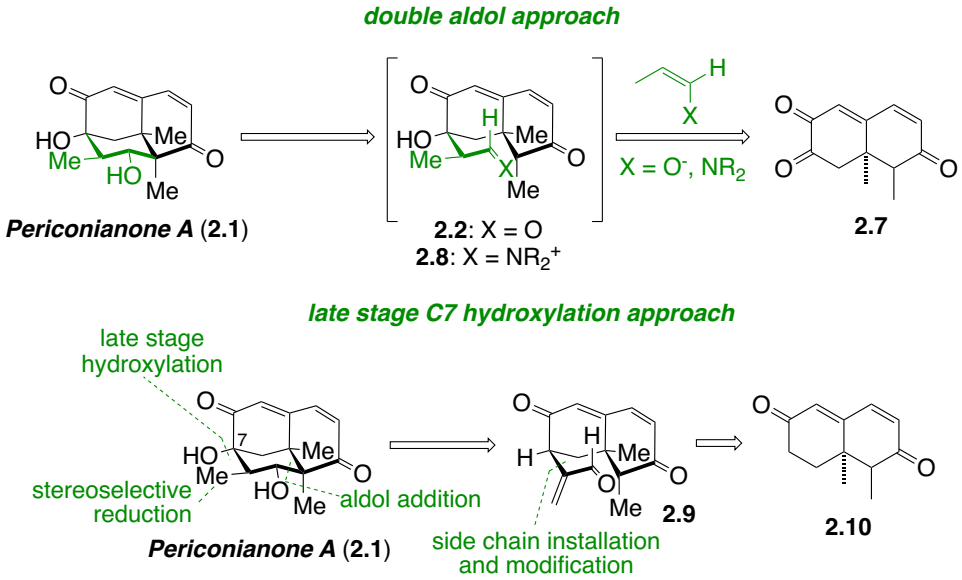
The pathway for the biosynthesis of periconianone A as proposed by J. Dai and co-workers[100] starts from an eremophilane derived precursor (**2.3**) and forms the aldehyde **2.4** by several oxidation events. This intermediate can either be oxidized to the carboxylic acid at C12 to form periconianone B (**2.5**), which was isolated from the same extracts as periconianone A, or hydroxylated at C7 to form the intermediate **2.2**. Retro-aldol reaction of this intermediate leads to the known natural product botryosphaeridione (**2.6**), which was also isolated from the same extracts. Alternatively, an intramolecular aldol addition joins C4 and C12 to form periconianone A (**2.1**).

[107] D. W. Christianson, *Chem. Rev.* **2006**, *106*, 3412-3442.

[108] E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 11943-11948.

2.1.2 Strategic Considerations and Aim of this Project

In our retrosynthetic proposal, we elaborated a synthetic route targeting the highly oxidized eremophilane bicycle **2.2** or a less oxidized precursor in order to test the feasibility of the proposed biogenetic C-ring cyclization by intramolecular aldol addition. Keeping in mind the lability of β-hydroxy aldehyde intermediate **2.2**, which is prone to undergo elimination and retro-aldol reactions, two different routes were designed. The first route involves a double aldol reaction starting from tricarbonyl compound **2.7** with **2.2**/**2.8** as intermediate; the second route features a late stage C7 hydroxylation after construction of the tricarbocyclic skeleton by aldol addition. A potential precursor of the latter approach might be the α,β-unsaturated aldehyde **2.9**, whose double bond could be stereoselectively reduced after aldol cyclization. For the installation of the side chain at C7, we envisioned a stepwise protocol of allylation, oxidative cleavage and methenylation starting from the diene dione **2.10** (Scheme 2.2).



Scheme 2.2: Retrosynthetic analysis of periconianone A (**2.1**) involving either a double aldol approach from tricarbonyl compound **2.7** or a stepwise approach by late stage hydroxylation at C7, stereoselective installation of the C13 methyl group as well as installation and modification of the C7 side chain prior to aldol cyclization.

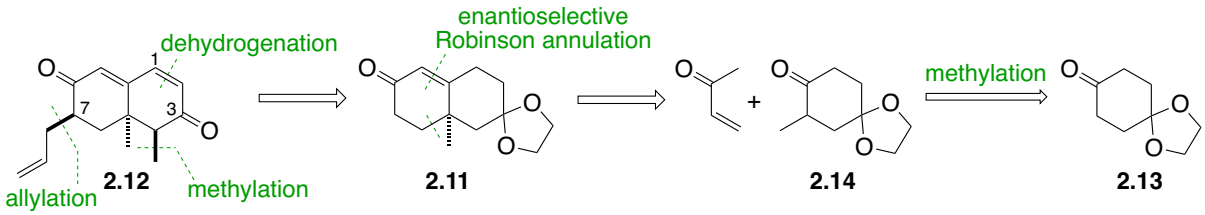
With this concise synthetic route to periconianone A (**2.1**) elaborated, we envisioned that we could gain synthetic access to structurally diverse derivatives of the natural product for SAR studies with the aim to identify the pharmacophore unit and finally synthesize more potent neural anti-inflammatory active agents.

2.2 Results and Discussion

2.2.1 Construction of the AB-Ring System

2.2.1.1 1st Approach

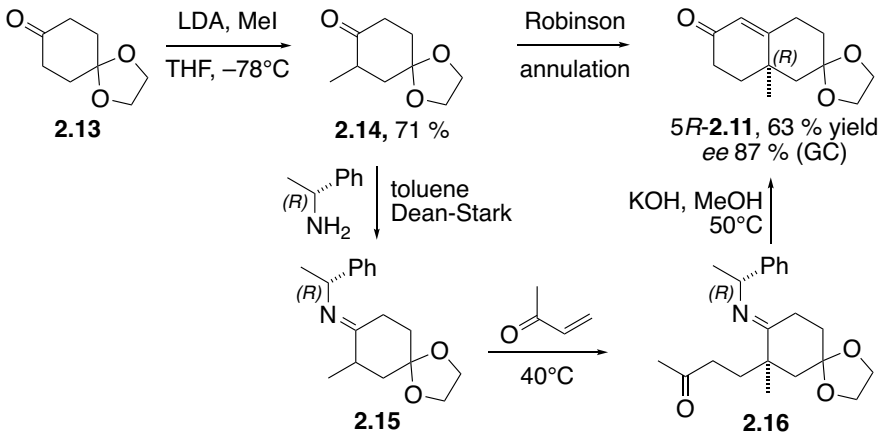
In the first approach towards the AB-ring system of periconianone A, we aimed to apply the Pfau-d'Angelo method (see section 1.4.1.3) to synthesize the mono-protected octalone **2.11**.[77,109] Allylation at C7, methylation at C4 and dehydrogenation of the C1–C2 bond after ketal deprotection of the carbonyl group at C3 (Scheme 2.3) would deliver the almost fully substituted AB-ring system **2.12**. The major advantages of this route are its conciseness with only eight synthetic steps necessary to obtain the allylated octalone **2.12**, and the use of only one protecting group. We were aware that introduction of the methyl group at C4 might be challenging due to steric interactions, mainly with the substituents on the neighboring quaternary carbon center at C5.



Scheme 2.3: First retrosynthetic analysis of the AB-ring system of periconianone A (**2.1**).

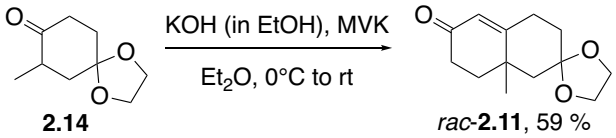
The synthesis commenced with α-methylation of mono-protected 1,4-cyclohexadione (**2.13**). Deprotonation with LDA in THF and subsequent addition of methyl iodide to the reaction mixture formed the desired methylated product in 71 % yield (Scheme 2.4). Reaction of the obtained α-methylated ketone **2.14** with *R*-1-phenylethylamine under Dean-Stark conditions gave the chiral imine **2.15**, which was subsequently reacted in an enantioselective Michael addition to MVK. The alkylated imine **2.16** was then hydrolyzed by methanolic KOH and underwent aldol condensation under the same reaction conditions to form the desired octalone **2.11** in an overall yield of 63 %, starting from **2.14**.[109]

[109] M. Pfau, I. Jabin, G. Revial, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1935-1936.



Scheme 2.4: Asymmetric synthesis of octalone **2.11** by Robinson annulation *via* chiral imine **2.15**.

Purification of octalone **2.11** proved to be challenging: after column chromatography had been performed twice, the compound still contained impurities, noticeable by a yellowish color and misfitting integrals in the ^{1}H NMR spectrum. On a small scale (50 mg), we were able to get rid of the yellow color by filtration of an ethereal solution of this compound over graphite. However, on a larger scale (> 1 g) this procedure was not reproducible and the yellow color persisted after filtration over graphite or activated charcoal. After screening different solvent systems for recrystallization, the best results were obtained by dissolving the compound in a 1:1 mixture of hexane and diethyl ether at reflux, followed by slowly cooling to room temperature to form colorless needles. The enantiomeric excess of octalone **2.11** was 87 %, as determined by chiral gas chromatography. As a reference, racemic **2.11** was synthesized in 59 % yield by a one-step Robinson annulation procedure using KOH and MVK in diethyl ether (Scheme 2.5).[110]

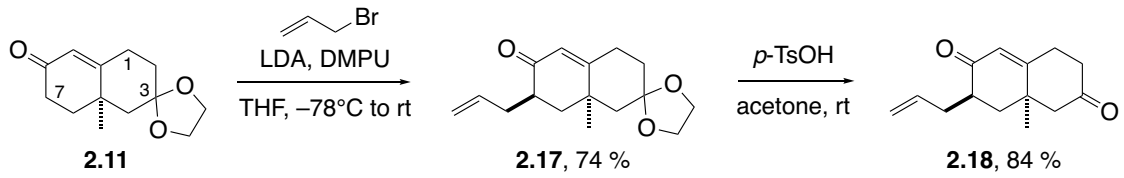


Scheme 2.5: Racemic synthesis of octalone **2.11**.

With this robust and short route to easily access the bicyclic system, the stage was set to investigate the functionalization of the octalone core of **2.11**. Since we needed to functionalize both C4 and C7 with alkyl substituents, our plan was to install the allyl group at C7 first, before the ketal protecting group was removed in order to methylate the C4 position. With minor modifications to a published procedure, *i.e.* using freshly distilled DMPU and applying a higher

[110] B. M. Trost, H. Hiemstra, *Tetrahedron* **1986**, *42*, 3323-3332.

number of equivalents of LDA (1.5 equiv. instead of 1.1 equiv.),[89] we successfully introduced the allyl side chain to form allylated octalone **2.17** in 74 % yield (Scheme 2.6).



Scheme 2.6: Allylation of octalone **2.11** and ketal deprotection.

The ketal was hydrolyzed in the presence of *p*-toluenesulfonic acid in catalytic amount to give the bicyclic enedione **2.18** in 80 % yield. We envisioned installation of the methyl group at C4 by deprotonation at the α-position of the C3 carbonyl moiety. In order to avoid deprotonation and undesired functionalization at C2 of **2.18**, we aimed to dehydrogenate the C1–C2 bond prior to C4 alkylation. The screened conditions are summarized in Table 2.1: we first investigated organoselenation at the C2 position, followed by oxidation and selenoxide elimination.[111] However, deprotonation in order to form the kinetic enolate of **2.18** by LiHMDS (entry 1) or LDA (entry 2), followed by addition of PhSeBr only resulted in a complex mixture, as monitored by ^{1}H NMR spectroscopy. Therefore, we investigated if the desired enolate might be formed by trapping the deprotonated species with TMSCl (entry 3) or TESCl (entry 4). In the former reaction, only starting material was isolated, possibly due to hydrolysis upon workup. The reaction using TESCl showed only low conversion and we obtained traces of two differently silylated compounds after column chromatography, indicating deprotonation not exclusively taking place at the C2 position. When **2.18** was treated with the bulkier lithium tetramethylpiperidide (LTMP, entry 5) as base, only 10 % conversion (^{1}H NMR of the crude mixture) to a silylated compound was observed. Applying a modified Saegusa-Ito protocol using $Pd(TFA)_2$ and O_2 in DMSO at 80°C only led to a complex mixture (entry 6).[112] Therefore, we started to investigate hypervalent iodine(V) reagents for the dehydrogenation of ketone **2.18** to the diene dione **2.19**. K. C. Nicolaou and co-workers showed that the combination of 2-iodobenzoic acid (IBX) and a Lewis base oxidizes a variety of ketones and aldehydes to the corresponding α,β-unsaturated compounds at room temperature.[113] However, applying the reported reaction conditions on our substrate, *viz.* stirring the reaction mixture with IBX and *p*-methoxypyridine *N*-oxide (MPO) in DMSO at ambient temperature, did not bring about the

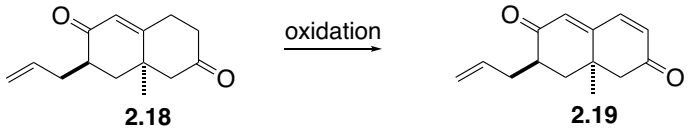
[111] H. J. Reich, J. M. Renga, I. L. Reich, *J. Am. Chem. Soc.* **1975**, *97*, 5434-5447.

[112] T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 14566-14569.

[113] K. C. Nicolaou, T. Montagnon, P. S. Baran, *Angew. Chem. Int. Ed.* **2002**, *41*, 993-996; K. C. Nicolaou, D. L. F. Gray, T. Montagnon, S. T. Harrison, *Angew. Chem. Int. Ed.* **2002**, *41*, 996-1000.

desired conversion. Neither did heating the reaction mixture to 40°C initiate conversion (entry 7).

Table 2.1: Screening conditions for the dehydrogenation of **2.18**.



2.18 **2.19**

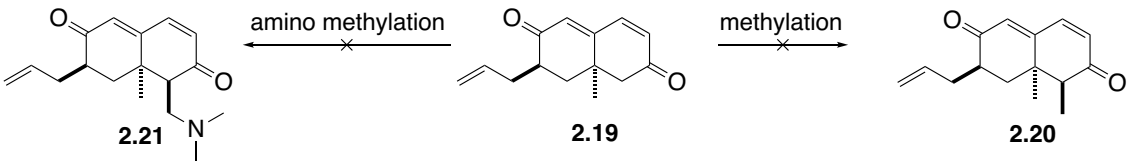
	reagent	solvent	temperature	time	scale	observations[a]
1	LiHMDS then PhSeBr	THF	–78°C	1 h 2 h	5 mg	complex mixture
2	LDA then PhSeBr	THF	–78°C	1 h 2 h	5 mg	complex mixture
3	LDA, TMSCl	THF	–78°C	1.5 h	5 mg	no conversion; hydrolyzed during workup
4	LDA, TESCl	THF	–78°C	1.5 h	5 mg	low conversion to unknown compounds
5	LTMP, TESCl	THF	–78°C	1.5 h	5 mg	low conversion to unknown compounds
6	$Pd(TFA)_2$, O_2	DMSO	80°C	14 h	5 mg	complex mixture
7	IBX (3.0 equiv.), MPO (3.0 equiv.)	DMSO	rt to 40°C	2 d at rt 1 d at 40°C	4 mg	no conversion
8	IBX (3.0 equiv.), MPO (3.0 equiv.)	DMSO	45°C to 60°C	30 min at 45°C o.n. at 60°C	10 mg	30 % conversion to **2.19** without significant side product formation
9	IBX (3.0 equiv.+ 2.0 equiv.), MPO (3.0 equiv.)	DMSO	45°C to 60°C	30 min at 45°C 32 h at 60°C	10 mg	3:1 (**2.19**/**2.18**) formation of side products
10	IBX (3.0 equiv.)[b], MPO (3.0 equiv.)	DMSO	45°C	3 d	10 mg	2:1 (**2.19**/**2.18**) formation of side products
11	IBX (3.0 equiv.)[b], MPO (3.0 equiv.)	DMSO	45°C	2 d	100 mg	4:3 (**2.19**/**2.18**) formation of side products 23 % **2.19** (42 % brsm)[c]
12	IBX (6.0 equiv.)[b], MPO (6.0 equiv.)	DMSO	45°C	1 d	10 mg	11:3 (**2.19**/**2.18**) less formation of side products

[a] monitored by ^{1}H NMR spectroscopy; [b] freshly prepared IBX[114] was used; [c] isolated yield after column chromatography.

We were thus pleased to find 30 % conversion to the desired diene dione **2.19** without significant side product formation at a reaction temperature of 60°C, as monitored by ^{1}H NMR spectroscopy (entry 8). Prolonged reaction time or further addition of IBX did not lead to increased product formation, but rather to more side products (entry 9). When freshly prepared IBX[114] was used, conversion at a lower temperature of 45°C was observed (entry 10). Upscaling

[114] M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537-4538.

this reaction led to an isolated yield of 23 % for the desired diene dione **2.19** and 19 % of recovered starting material **2.18** (entry 11). In order to further optimize the conversion to the desired product and suppress side product formation, we investigated conditions with the aim to shorten the reaction time. Using double amounts of both reagents IBX and MPO from the beginning did indeed accelerate the reaction and furnish more of the desired product with less side products on a small scale (entry 12).

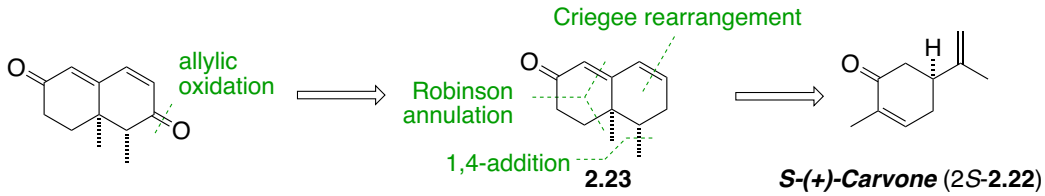


Scheme 2.7: Attempts to introduce the one-carbon moiety at C4 of **2.19**.

With diene dione **2.19** in hand, we started to investigate the functionalization at C4 (Scheme 2.7). Unfortunately, neither methylation (LiHMDS, MeI, DMPU) nor aminomethylation (LiHMDS, Eschenmoser's salt) of the enolate derived from **2.19** was successful and did not form the desired compounds **2.20** or **2.21**, respectively. Deuteration experiments were performed by adding two equivalents of LiHMDS to a solution of **2.19** in THF at –78°C, followed by quenching with CD_3OD. Analysis of the crude mixture by ^1H NMR spectroscopy revealed that deprotonation took place at the C4 as well as the C7 position. However, electrophiles did not add to the C4 position. This result in combination with the sluggish dehydrogenation reaction (Table 2.1) prompted us to abandon this approach.

2.2.1.2 2nd Approach

After the first approach had revealed C4 in **2.19** to be inaccessible towards alkylation, we designed a new strategy with the aim to introduce the methyl substituent at C4 prior to B-ring formation (Scheme 2.8). As outlined in the introduction part (see section 1.4.1.2), elegant syntheses of functionalized octalones are described by the groups of P. Duhamel[68] and A. de Groot[74] starting from the chiral pool-derived and commercially available monoterpene *S*-carvone (2*S*-**2.22**). The latter group has already developed a five-step procedure for the synthesis of dienone **2.23**. Conjugate addition for the installation of a carbon substituent at C4 was followed by a two-step Robinson annulation procedure. The isopropenyl group, which served as a removable directing group for stereoselective synthesis, was then removed by a Criegee rearrangement.[76] After obtaining octalone **2.23**, we envisioned to introduce the missing oxygen substituent at C3 by allylic oxidation.



Scheme 2.8: Second retrosynthetic analysis of the AB-ring system of periconianone A (**2.1**).

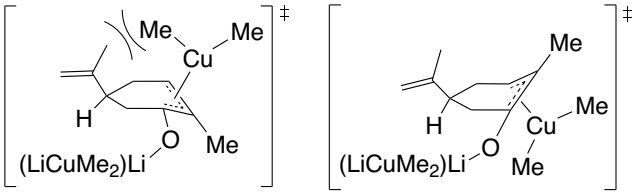
The synthesis started by conjugate addition of methyl cuprate to the enone moiety of *S*-carvone, followed by subsequent trapping of the resulting enolate as the TMS enol ether. The described procedures for this reaction sequence comprise addition of MeMgBr to a solution of *S*-carvone (2*S*-**2.22**) in the presence of a catalytic amount of copper bromide dimethyl sulfide complex ($CuBr \cdot SMe_2$), TMSCl and hexamethylphosphoric triamide (HMPA) at –40°C. These conditions proved laborious, involved the use of carcinogenic and mutagenic HMPA and only moderate yields (51 %; lit. 86 %, *de* 86 %) were obtained for the desired silyl enol ether. Therefore, we tested an alternative protocol described by the group of M. T. Reetz,[115] based on studies by M. S. Kharasch *et al.*[116] using catalytic amounts of cost-efficient CuI and LiCl. These metal salts are mixed in THF to give a homogeneous solution of the active copper ate-complex $Li_2[CuX_3]$. After cooling to 0°C, *S*-carvone (2*S*-**2.22**) and TMSCl were added, followed by MeMgBr. This procedure led to quantitative conversion to the desired silyl enol ether (by ^{1}H NMR). After silica gel flash column chromatography, we isolated the pure product **2.24** in 68 % yield (Scheme 2.9) and a diastereomeric ratio of >10.1. The moderate yield after purification can be explained by hydrolysis during column chromatography and use of crude **2.24** for the following reaction step might be considered as an alternative. Complete selectivity in favor for the *trans*-2,4-substituted product was observed, even though this diastereoisomer (one axial substituent) is supposed to be higher in energy compared to the *cis*-product (both substituents equatorial). It has already been reported in 1966 that stereoselectivity in the conjugate addition to 5-substituted cyclohexanones to yield 3,5-disubstituted derivatives is not solely governed by thermodynamic arguments regarding the relative stability of the product stereoisomers, but also by the energy levels of the respective transitions states.[117] Later, transition states for this transformation comprising a trihapto coordination (η^3) of the allyl ligand to the central copper ion derived from the intermediate cuprate complexes shown in

[115] M. T. Reetz, A. Kindler, *J. Organomet. Chem.* **1995**, *502*, C5-C7.

[116] M. S. Kharasch, P. O. Tawney, *J. Am. Chem. Soc.* **1941**, *63*, 2308-2316.

[117] N. L. Allinger, C. K. Riew, *Tetrahedron Lett.* **1966**, *7*, 1269-1272.

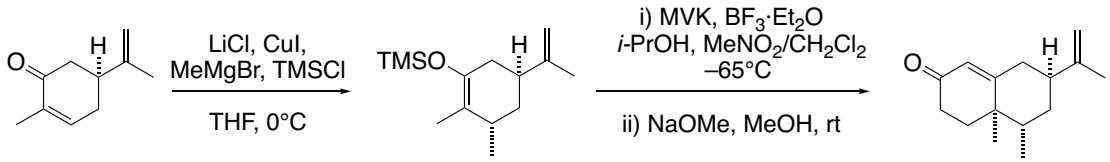
Figure 2.2 was proposed.[118] The transition state leading to the *cis*-2,4-substituted cyclohexanone (*cis*-**2.26**) is unfavored due to steric repulsion between the isopropenyl group on the substrate and the methyl ligand bound to the copper ion. This steric interaction is nonexistent in the transition state leading to the *trans*-2,4-substituted cyclohexanone (*trans*-**2.26**), whose formation is thus favored.



cis-**2.26** (disfavored) *trans*-**2.26** (favored)

Figure 2.2: η^3-Allyl cuprate complexes as intermediates in the conjugate addition of methyl cuprate to *S*-carvone rationalizing the observed *trans*-selectivity with respect to the alkyl substituents at C2 and C4.

With TMS enol ether in hand, Lewis acid-mediated Michael addition using $BF_3 \cdot OEt_2$ was followed by a basic aldol condensation catalyzed by sodium methoxide to give the desired octalone **2.25** in 61 % yield and a diastereomeric ratio of >10:1 over two steps. This exclusive *cis*-selectivity with respect to the methyl groups at C4 and C5 can be explained by the conformer structures of the starting material as shown in Scheme 2.10.



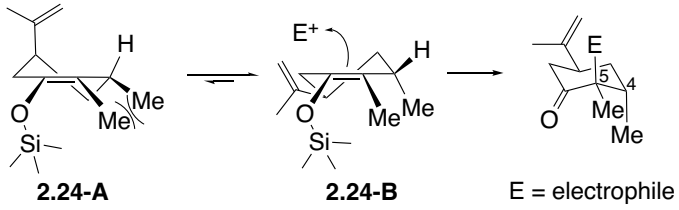
S-(+)-Carvone (2*S*-**2.22**) **2.24**, 68 %, *dr* > 10:1 **2.25**, 61 % over two steps *dr* > 10:1

Scheme 2.9: Conjugate addition and Robinson annulation sequence for the synthesis of octalone derivative **2.25**.

Due to $A^{1,2}$ strain between the methyl groups at position C4 and C5, the transition state derived from conformer **2.24-B** of the silyl enol ether starting material is preferred over the one derived from **2.24-A**.[119] Additionally, the isopropenyl group favors an equatorial orientation as in **2.24-B**, and together with the electrophilic attack taking place from the less shielded *Re* face of the enolate's α-carbon leads to the desired diketo diastereoisomer.

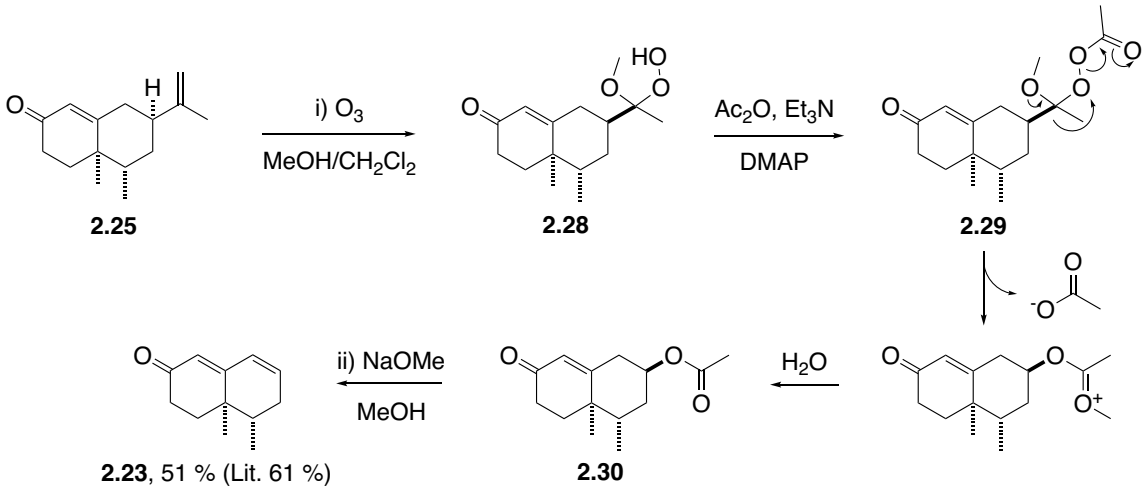
[118] E. J. Corey, F. J. Hannon, *Tetrahedron Lett.* **1990**, *31*, 1393-1396; R. Imbos, A. J. Minnaard, B. L. Feringa, *Tetrahedron* **2001**, *57*, 2485-2489; S. R. Krauss, S. G. Smith, *J. Am. Chem. Soc.* **1981**, *103*, 141-148.

[119] F. Johnson, *Chem. Rev.* **1968**, *68*, 375-413.



Scheme 2.10: A[1,2] strain to explain the *cis*-selectivity with respective to the methyl groups at C4 and C5.

The isopropenyl group of octalone **2.25** was then cleaved by a Criegee rearrangement reaction as shown in Scheme 2.11.[76] Mechanistically, ozonolysis of **2.25** in a MeOH/CH_2Cl_2 mixture forms the peroxy acetal intermediate **2.28** *via* a primary ozonide. The peroxide moiety is then acetylated using acetic anhydride, Et_3N and DMAP. This intermediate of an acetylated peroxy acetal (**2.29**) can rearrange to release acetate and form the ester **2.30** after hydrolysis, which can be eliminated under basic conditions. This procedure gave the desired dienone **2.23** in 51 % yield (Scheme 2.11).



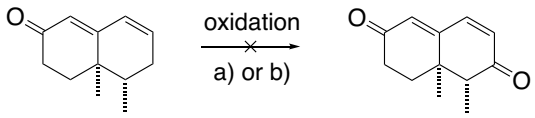
Scheme 2.11: Criegee rearrangement mechanism for the synthesis of dienone **2.23**.

With octalone **2.23** in hand, we started to investigate procedures for the oxidation of the allylic C3 position. Unfortunately, protocols involving either radical or ionic pathways were not successful for octalone **2.23** (Scheme 2.12). $Co(acac)_2$-catalyzed allylic oxidation (*t*-BuOOH, acetone, rt), which had previously been applied for the oxidation of various electron-poor enones,[120] resulted in formation of a complex mixture. Riley oxidation[121] led to an unknown side product lacking a ketone or enone group, since no signal was detected in the appropriate chemical shift region in the ^{13}C NMR spectrum. However, a signal at 184 ppm

[120] X. Q. Han, Z. Y. Zhou, C. Wan, Y. M. Xiao, Z. H. Qin, *Synthesis* **2013**, *45*, 615-620.

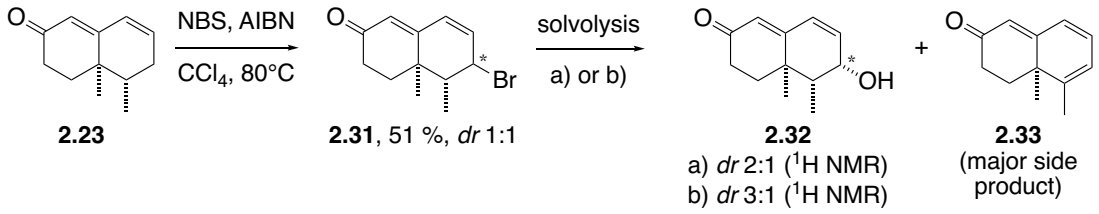
[121] H. L. Riley, J. F. Morley, N. A. C. Friend, *J. Chem. Soc.* **1932**, 1875-1883.

indicated an ester moiety present in this unidentified compound. It is known that conjugated bicyclo[4.4.0]decandienones react sluggishly in allylic oxidation reactions. Recently, an allylic oxidation procedure of C7 functionalized octalones using PDC (pyridinium dichromate) and *t*-BuOOH in benzene gave only 28 % yield of the desired oxidized diene dione, as described by the group of D. S. Reddy (see section 1.4.2.2).[99]



Scheme 2.12: Attempts at the allylic oxidation of **2.23**. Reaction conditions: a) $Co(acac)_2$, *t*-BuOOH, acetone, rt; b) SeO_2, dioxane, 100°C.

We therefore decided to brominate the C3 position with the aim of replacing the bromide by a hydroxy group in an additional solvolysis step. Bromination using *N*-bromosuccinimide (NBS) and azobisisobutyronitrile (AIBN) in CCl_4 at 80°C furnished the desired brominated dienone **2.31** as a diastereomeric 1:1 mixture in 51 % yield (Scheme 2.13). The choice of reaction time had substantial influence on the product's diastereomeric ratio and an experiment with a shorter reaction time of five hours, instead of 18 hours, gave a *dr* of 7:3. This indicates that the bromination might be stereoselective and epimerization on prolonged heating takes place. Additionally, dibromination of the C1=C2 double bond as a side reaction was observed. Solvolysis was performed by stirring the synthesized bromide **2.31** with silver(I) salts in a mixture of acetone and water in the dark.



2.23 | **2.31**, 51 %, *dr* 1:1 | **2.32** a) *dr* 2:1 (^{1}H NMR) b) *dr* 3:1 (^{1}H NMR) | **2.33** (major side product)

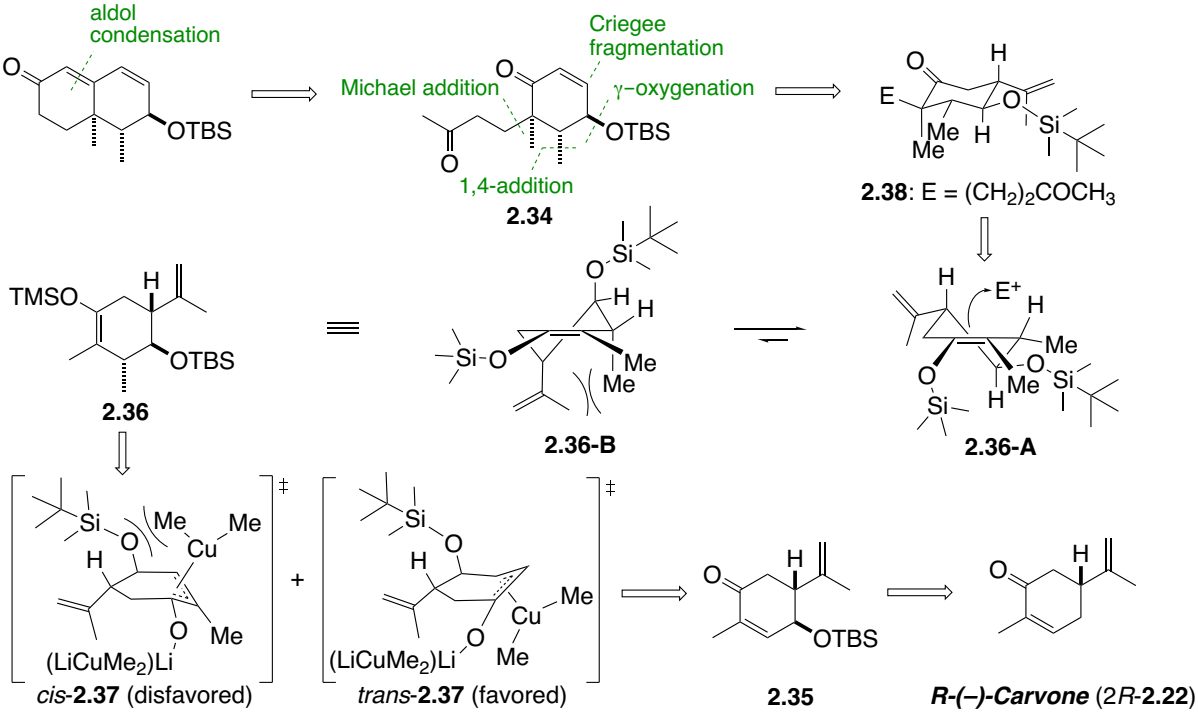
Scheme 2.13: Bromination of **2.23** and subsequent solvolysis. Reaction conditions: a) Ag_2CO_3, acetone/H_2O (8:1), rt; b) CF_3COOAg, acetone/H_2O (5:1), rt.

The desired C3 hydroxylated octalone **2.32** was formed along with the elimination product **2.33** as the major side product. Due to the low conversion (observed by ^{1}H NMR spectroscopy) of the solvolysis step and based on the unsuitability of the dienone moiety in the ensuing steps of this synthetic route observed later on, we did not further investigate this strategy. The C1=C2 double bond might be more suitable to be installed later on in the synthesis. Additionally, we had in parallel started to investigate a 3rd approach towards the total

synthesis of periconianone A featuring installation of the C3 oxygen substituent on the monocyclic compound, which gave much more promising results.

2.2.1.3 3rd Approach

In parallel to the second approach, we investigated if the C3 oxygen substituent might be more readily installed at the beginning of the synthesis. Therefore, we envisioned to modify the second approach by installation of a hydroxy group in the γ-position of carvone and to probe the feasibility of A-ring modification on this hydroxylated substrate. In order to stereoselectively elaborate the C2, C3 and C4 positions, we outlined the retrosynthetic pathway from the targeted diketo compound **2.34** given in Scheme 2.14, considering the stereoselectivity of each transformation for the installation of the appropriate substituents.



Scheme 2.14: Third retrosynthetic analysis of the AB-ring system of periconianone A (**2.1**) starting from *R*-carvone (2*R*-**2.22**).

After the hydroxy group at C3 will be installed and protected, 1,4-addition comparable to the 2nd approach will methylate C4. In the conjugate addition of methyl cuprate to *S*-carvone (see previous section), we argued that steric repulsion between the isopropenyl group and the methyl ligands of the cuprate complex disfavors one of the transition states, leading to the observed selectivity for a *trans*-2,4 substitution in **2.24**. In the case of protected γ-hydroxy carvone derivative **2.35**, we assume that steric repulsion of the methyl ligands on the cuprate with the OTBS group on the substrate might be more pronounced than the steric interaction

with the isopropenyl group. Therefore, we propose the transition states featuring trihapto coordination of the copper ion shown in Scheme 2.14, and the favored *trans*-**2.37** leading to the desired *trans*-3,4 substitution product **2.36**. To this end, we intended to start from the *R*-enantiomer of carvone (2*R*-**2.22**). Both *S*- and *R*-carvone have been widely used as sustainable starting materials in preparation of enantiopure natural products[122,123] and starting with the more cost-efficient *R*-enantiomer is highly desirable. The selectivity in the Michael reaction of TMS enol ether **2.36** to MVK to give the desired diketo compound **2.38** was predicted by an all-equatorial orientation of the substituents at C2, C3 and C4 to minimize the $A^{1,3}$ strain between the C2 isopropenyl and the C4 methyl groups as shown by conformer **2.36-A**.

The synthetic route started with a literature known two-step protocol (Scheme 2.15):[124] preparation of the thermodynamic TMS enol ether **2.39** was achieved by regioselective γ-deprotonation of *R*-carvone using the Kharasch reagent.[116,125] The reduction of iron(III) chloride to a lower-valent iron(II) species using methyl lithium or methyl Grignard reagent accompanied by formation of methane (ca. 10 %, by reaction of the concomitantly formed methyl radical with the solvent) or ethane (ca. 90 %, by recombination of methyl radicals) had already been described earlier.[126] However, it was not until recently that the red solid, isolated after mixing iron(III) chloride with methyl lithium at –30°C followed by removal of lithium chloride and the solvent, could be crystallized and fully characterized by the group of A. Fürstner.[127] Upon slow cooling of a saturated solution of the formed compound in diethyl ether from –40°C to –78°C, yellow-orange plates were obtained, whose single crystal X-ray analysis showed a dianionic homoleptic iron(II) complex with four methyl ligands in an almost ideal tetrahedral arrangement with $[Li(OEt_2)]^+$ as counterion and the molecular formula $[(Me_4Fe)(MeLi)][Li(OEt_2)]_2$. Treatment of dihydrocarvone with either this reagent or with $FeCl_3$ and MeMgX (as described in the original procedure)[128] gave identical results after

[122] For reviews: Z. G. Brill, M. L. Condakes, C. P. Ting, T. J. Maimone, *Chem. Rev.* **2017**, *117*, 11753-11795; F. Z. Macaev, in Stud. Nat. Prod. Chem., *Vol. 39* (Ed.: A.-u. Rahman), Elsevier, **2013**, pp. 233-267.

[123] For recent examples: P. Finkbeiner, K. Murai, M. Röpke, R. Sarpong, *J. Am. Chem. Soc.* **2017**, *139*, 11349-11352; D. Chen, P. A. Evans, *J. Am. Chem. Soc.* **2017**, *139*, 6046-6049; L. J. Nannini, S. J. Nemat, E. M. Carreira, *Angew. Chem. Int. Ed.* **2018**, *57*, 823-826; A. W. Schuppe, D. Huang, Y. Chen, T. R. Newhouse, *J. Am. Chem. Soc.* **2018**, *140*, 2062-2066.

[124] G.-Q. Tian, J. Yang, K. Rosa-Perez, *Org. Lett.* **2010**, *12*, 5072-5074; J. H. Huang, J. R. Yang, J. Zhang, J. Yang, *Org. Biomol. Chem.* **2013**, *11*, 3212-3222.

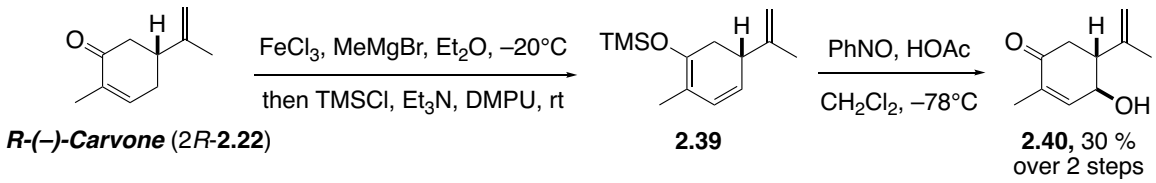
[125] M. E. Krafft, R. A. Holton, *J. Am. Chem. Soc.* **1984**, *106*, 7619-7621; F. C. E. Saraber, A. Baranovsky, B. J. M. Jansen, M. A. Posthumus, A. de Groot, *Tetrahedron* **2006**, *62*, 1726-1742.

[126] H. J. Spiegl, G. Groh, H. J. Berthold, *Z. Anorg. Allg. Chem.* **1973**, *398*, 225-230; H. J. Berthold, H. J. Spiegl, *Z. Anorg. Allg. Chem.* **1972**, *391*, 193-202.

[127] A. Fürstner, H. Krause, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 440-444.

[128] S. M. Ceccarelli, U. Piarulli, C. Gennari, *Tetrahedron* **2001**, *57*, 8531-8542.

quenching the reaction with TMSCl and Et_3N, which strongly corroborates the "Kharasch reagent" to match the described iron "super-ate" complex.



R-(–)-Carvone (2*R*-**2.22**) **2.39** **2.40,** 30 % over 2 steps

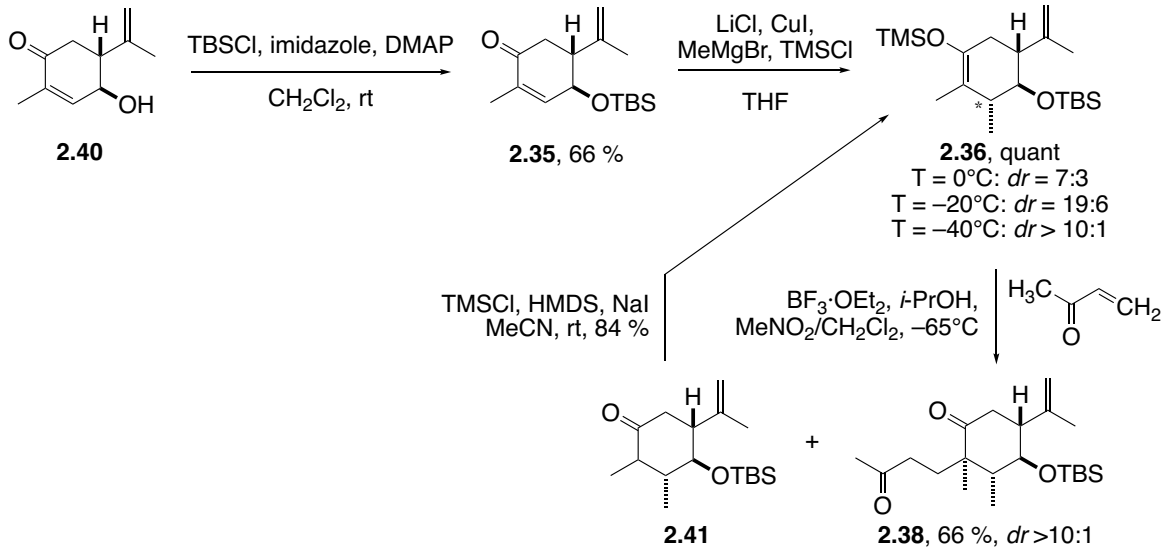
Scheme 2.15: Synthesis of γ-hydroxy carvone (**2.40**) by a two-step literature procedure.[124]

TMS enol ether **2.39** was then treated with 2.4 equivalents of nitrosobenzene and acetic acid to form γ-hydroxy carvone (**2.40**) in 30 % yield over two steps. The yield of 60 % reported in literature could not be reproduced, which is in agreement with a recently published article by the group of M. A. Brimble.[129] Mechanistically, the first equivalent of the nitrosobenzene is attacked by the nucleophile **2.39** in a vinylogous Mukaiyama-type aldol reaction to form the corresponding γ-aminohydroxylated compound. The second equivalent of nitrosobenzene then reduces the formed *O*-substituted *N*-phenylhydroxylamine intermediate with dissociation of the O–N bond releasing the desired γ-hydroxy carvone (**2.40**) and *trans*-azoxybenzene.[130] Alternatively, γ-hydroxy carvone (**2.40**) was synthesized in a single-step procedure using a mixed copper-aluminum oxide catalyst and potassium *tert*-butoxide.[131] Unfortunately, we could only isolate 14 % of **2.40** when applying this literature procedure. The installed secondary alcohol was protected using TBSCl, imidazole and DMAP. The moderate yield of 66 % of **2.35** might be explained by impurities present in the starting material and separated at this stage of the total synthesis. When the same reaction conditions as for *S*-carvone (LiCl, CuI, MeMgBr, TMSCl, THF, 0°C) were used in the conjugate addition of methyl cuprate to C3-hydroxylated enone **2.35**, a diastereomeric mixture of 7:3 in favor of the desired isomer was obtained (Scheme 2.16). By carrying out the reaction at a lower temperature of –20°C instead of 0°C, we could increase this selectivity to 19:6, and at –40°C to >10:1. However, no conversion of the starting materials was observed at lower reaction temperatures (–50°C). The enolate formed after the addition of methyl cuprate was directly trapped by TMSCl to form the corresponding TMS enol ether **2.36**.

[129] J. G. Hubert, D. P. Furkert, M. A. Brimble, *J. Org. Chem.* **2015**, *80*, 2231-2239.

[130] D. B. Ramachary, C. F. Barbas, *Org. Lett.* **2005**, *7*, 1577-1580.

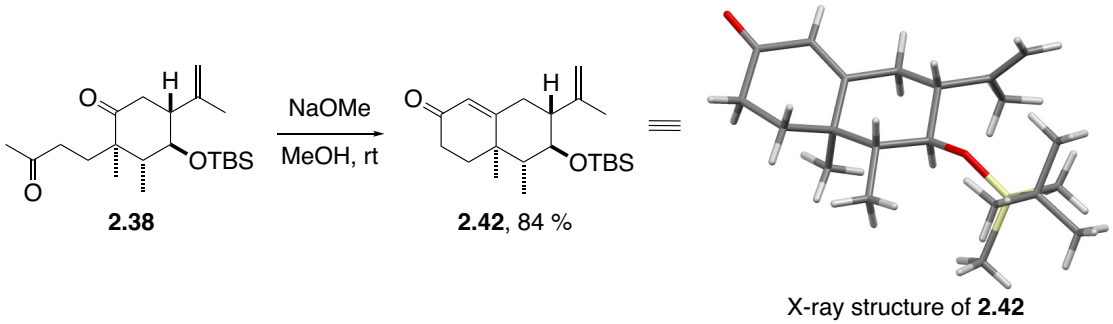
[131] A. L. García-Cabeza, R. Marín-Barrios, R. Azarken, F. J. Moreno-Dorado, M. J. Ortega, H. Vidal, J. M. Gatica, G. M. Massanet, F. M. Guerra, *Eur. J. Org. Chem.* **2013**, *2013*, 8307-8314.



Scheme 2.16: A-ring functionalization: TBS protection of the secondary C3 hydroxyl group; 1,4-addition at C4; Michael-addition on methyl vinyl ketone at C5.

With TMS enol ether **2.36** in hand, we investigated the Michael-addition step on this substrate: initial experiments were very low yielding and delivered mostly desilylated starting material **2.41**. Experiments that showed higher yields for the desired diketone **2.38** were not reproducible, which led us to carefully screen the reaction conditions. Briefly, we increased the quality of the reagents by distillation of $BF_3 \cdot OEt_2$ directly prior to the reaction and by the use of dry isopropanol as well as dry nitromethane. Addition of all the reagents was performed at –78°C, before warming to –65°C and carefully monitoring the reaction temperature. At lower reaction temperatures, no conversion took place and at higher temperatures (–20°C), increased desilylation was observed. In the procedure described by A. de Groot *et al.*,[74] the mixture of all reagents except for the Lewis acid $BF_3 \cdot OEt_2$ was stirred at –78°C for 30 minutes, before the latter was added. We found that during this time, significant desilylation took place. In consequence, we only stirred the other reagents for five minutes before adding $BF_3 \cdot OEt_2$. Furthermore, adding extra $BF_3 \cdot OEt_2$ (0.1 – 0.5 equiv.) after stirring for three to five hours had a positive influence on conversion. Combining these optimizations culminated in a yield of 66 % and a diastereomeric ratio of >10:1 for diketone **2.38**, along with formation of a diastereomeric mixture of desilylated starting material **2.41** as the only detectable side product. Re-silylation of this compound using TMSCl, HMDS and NaI in acetonitrile at room temperature delivered the silyl enol ether **2.36** in 84 % yield after flash column chromatography. To prevent hydrolysis during chromatography, only a short plug of silica was used to minimize the duration of compound/SiO_2 interaction.

With the fully substituted A-ring in hand, our next aim lay in constructing the B-ring and removing the isopropenyl group by a Criegee rearrangement. Aldol condensation of **2.38** using sodium methoxide gave the bicyclic compound **2.42** in 84 % yield, whose structure was confirmed by single-crystal X-ray analysis (Scheme 2.17).

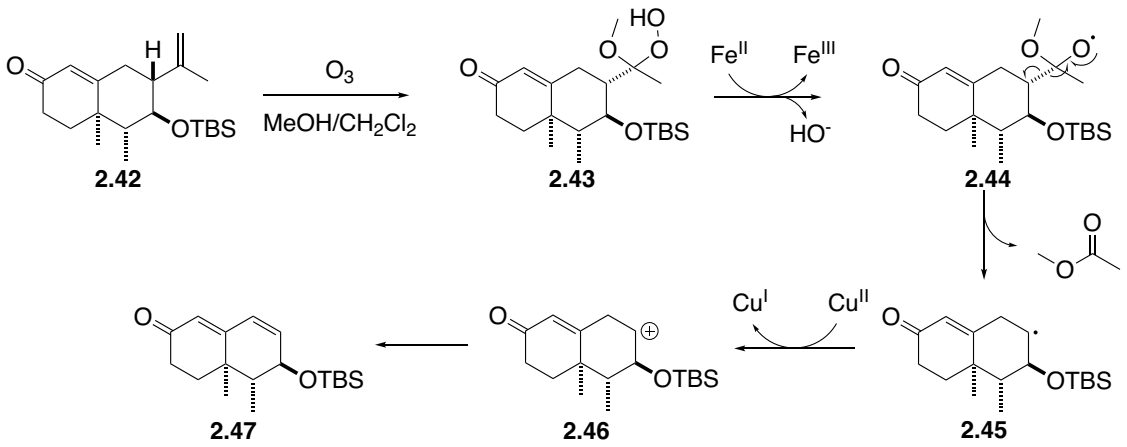


2.38 **2.42**, 84 %

Scheme 2.17: B-ring formation by an aldol condensation reaction, and single crystal X-ray structure of **2.42**.

However, removal of the isopropenyl moiety turned out to be very low-yielding on the bicyclic substrate **2.42** using either conditions triggering a Criegee rearrangement or a Criegee fragmentation pathway (Table 2.2). While the former transformation was discussed in section 2.2.1.2, the latter pathway was first described by the group of S. Schreiber[132] and mechanistic details are given in Scheme 2.18. Ozonolysis of the isopropenyl group leads to a primary ozonide, which is cleaved in a 1,3-dipolar cycloreversion to form formaldehyde and the carbonyl oxide. The carbonyl oxide is attacked by methanol to form peroxy acetal **2.43**. Transfer of an electron from Fe^{2+} to the peroxide function leads to dissociation of the O–O bond and formation of the oxy radical **2.44**. This radical is destabilized by an antibonding interaction with the neighboring methoxy group and easily forms the carbon-centered radical **2.45**. Oxidation of the radical at C2 to the corresponding carbocation was mediated by Cu^{2+} to form **2.46** and subsequent β-elimination results in the fragmentation product **2.47**.

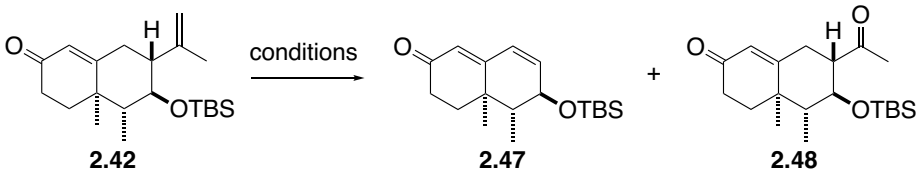
[132] S. L. Schreiber, *J. Am. Chem. Soc.* **1980**, *102*, 6163-6165; S. L. Schreiber, B. Hulin, W.-F. Liew, *Tetrahedron* **1986**, *42*, 2945-2950.



Scheme 2.18: Criegee fragmentation mechanism for octalone **2.42**.

With the same conditions as applied in the previous approach for octalone **2.25** (Table 2.2, entry 1), reaction of **2.42** yielded a mixture of the desired dienone **2.47** and methyl ketone **2.48** in a ratio of 2:7 along with some unidentified side products.

Table 2.2: Selected conditions for the Criegee rearrangement or fragmentation of **2.42** to **2.47**.



entry	reagent/catalyst	solvent	temperature	observations
1	i) O_3 then Ac_2O, Et_3N, DMAP ii) NaOMe	i) CH_2Cl_2/MeOH (5:1) ii) MeOH	i) –78°C then rt ii) rt	ii) **2.47**/**2.48** (2:7) and side products[a]
2	i) O_3 then Ac_2O, Et_3N, DMAP ii) NaOMe	i) CH_2Cl_2, MeOH (4 equiv.) ii) MeOH	i) –78°C then 0°C ii) rt	ii) **2.47**/**2.48** (1:4) and side products[a]
3	O_3 then $Cu(OAc)_2 \cdot H_2O$, $FeSO_4 \cdot 7H_2O$	CH_2Cl_2/MeOH (4:3)	–78°C then –20°C to rt	26 % **2.47**, 13 % **2.48**[b]

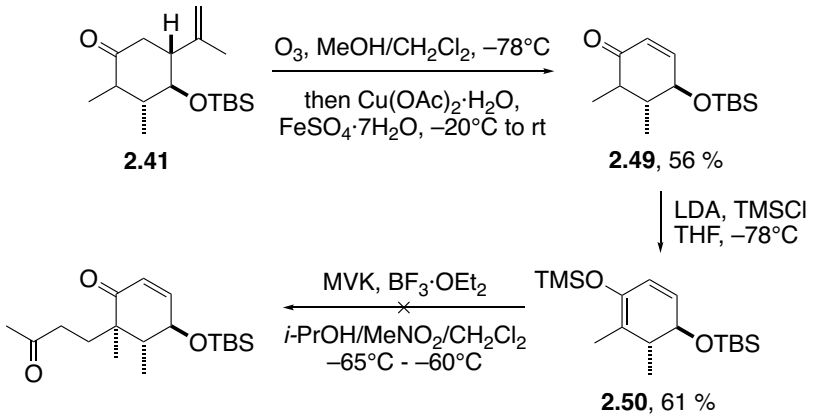
[a] monitored by ^{1}H NMR spectroscopy; [b] isolated yield after column chromatography.

During the optimization process of this transformation starting from epoxidized *S*-carvone,[133] A. R. Daniewski *et al.* found that adjusting the amount of methanol in the reaction mixture was the key for successfully triggering the Criegee rearrangement. To form the peroxy acetal and to avoid the formation of the thermally more stable secondary ozonide, methanol is crucial for the reaction. Cleanest conversion to the desired peroxy acetal was reported using only four equivalents of methanol. Unfortunately, following their protocol we observed an even

[133] A. R. Daniewski, L. M. Garofalo, S. D. Hutchings, M. M. Kabat, W. Liu, M. Okabe, R. Radinov, G. P. Yiannikouros, *J. Org. Chem.* **2002**, *67*, 1580-1587.

higher 1:4 ratio of **2.47**/**2.48** in favor for undesired **2.48** (entry 2). By applying the reported reaction conditions for the Criegee fragmentation with $Cu(OAc)_2 \cdot H_2O$ and $FeSO_4 \cdot 7H_2O$, the desired dienone **2.47** was formed in 26 % isolated yield (entry 3).[134] Treatment of the methyl ketone **2.48** with *m*-CPBA to bring about the conversion to the desired acetate *via* a Baeyer-Villiger oxidation was not successful either and resulted only in formation of a complex mixture.

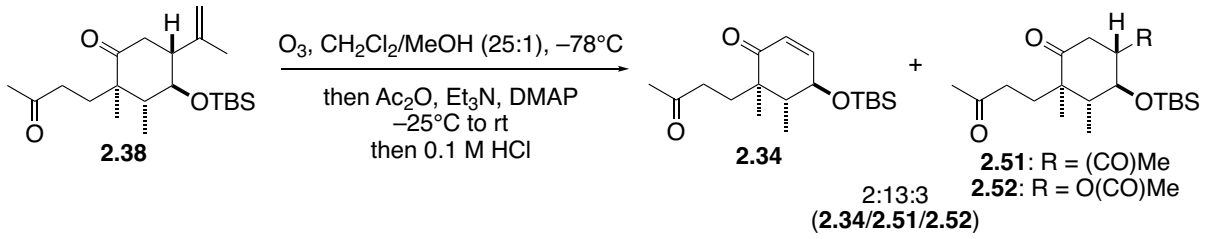
Instead of extending our screening efforts, we decided to investigate the removal of the isopropenyl group at an earlier stage of the synthetic route, *viz.* either right before the construction of the bicyclic structure or even before the Michael addition to methyl vinyl ketone. Drawback of the latter strategy is the necessity of additional silyl enol ether formation after removal of the isopropenyl group (**2.49** → **2.50**). However, we investigated both pathways in parallel as summarized in Scheme 2.19, Scheme 2.20 and Scheme 2.21.



Scheme 2.19: Attempted strategy comprising an early-stage Criegee fragmentation for the removal of the isopropenyl group.

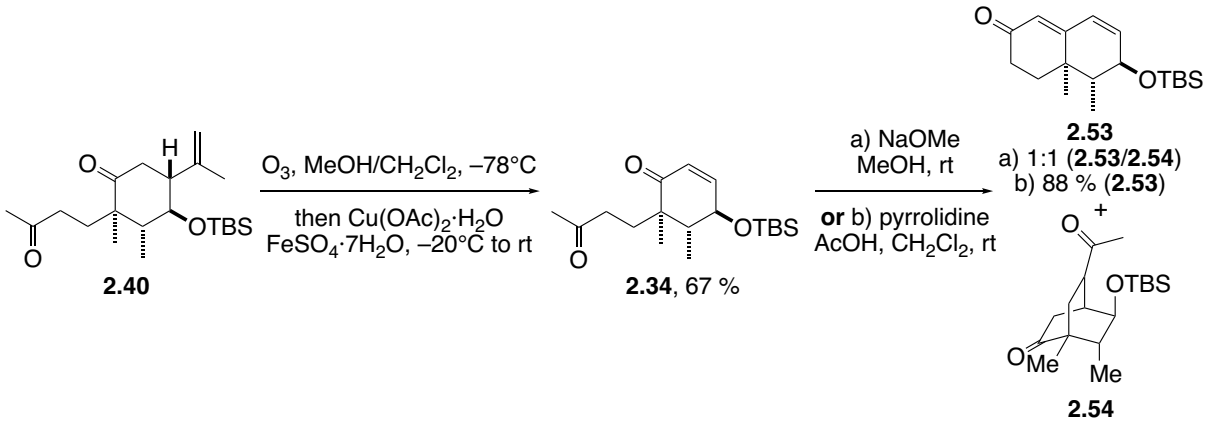
Criegee fragmentation of cyclohexanone **2.41** gave the desired enone **2.49** in a moderate yield of 56 %. Unfortunately, after forming the silyldienolether **2.50**, Michal addition to MVK only gave a complex mixture.

[134] X. L. Qi, J. T. Zhang, J. P. Feng, X. P. Cao, *Org. Biomol. Chem.* **2011**, *9*, 3817-3824; J. D. White, U. M. Grether, C.-S. Lee, *Org. Synth.* **2005**, *82*, 108-114.



Scheme 2.20: Criegee rearrangement of monocyclic compound **2.38**.

In a more elegant approach, we cleaved the isopropenyl group after Michael addition of **2.36** to MVK. Upon formation of the peroxy acetal derived from **2.38**, Criegee rearrangement (Ac_2O, Et_3N, DMAP) only gave minor amounts of the desired enone **2.34**, along with methyl ketone **2.51** and ester **2.52** as side products in a ratio of 2:13:3 (Scheme 2.20). Pleasingly, the conditions used for the Criegee fragmentation discussed earlier formed the desired enone **2.34** in 67 % isolated yield (Scheme 2.21).

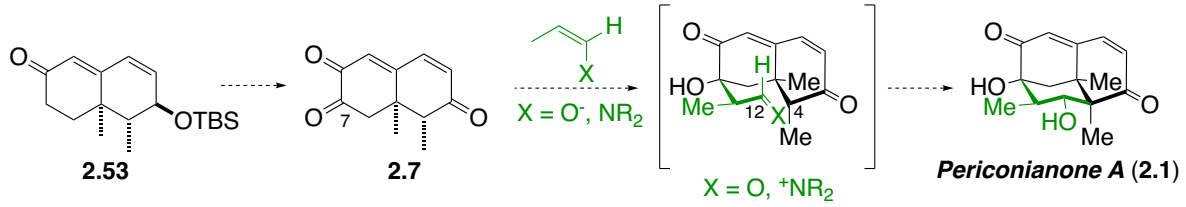


Scheme 2.21: Criegee fragmentation reaction and aldol cyclization to form the bicyclic dienone **2.53**.

Cyclization of enone **2.34** under basic conditions using NaOMe in MeOH resulted in a mixture of the desired aldol product **2.53** and the undesired Michael addition byproduct **2.54** in a mixture of 1:1. The concentration of base was found to have no influence on this ratio. Further screening of reaction conditions in order to favor formation of the desired condensation product culminated in employing enamine catalysis: stirring a mixture of enone, pyrrolidine and acetic acid in dichloromethane at room temperature gave the bicyclic dienone **2.53** in 88 % yield. With proline as catalyst, no conversion was observed at room temperature and only slow conversion without completion at 40°C, although 1.5 equivalents of the amino acid had been added to the reaction mixture.

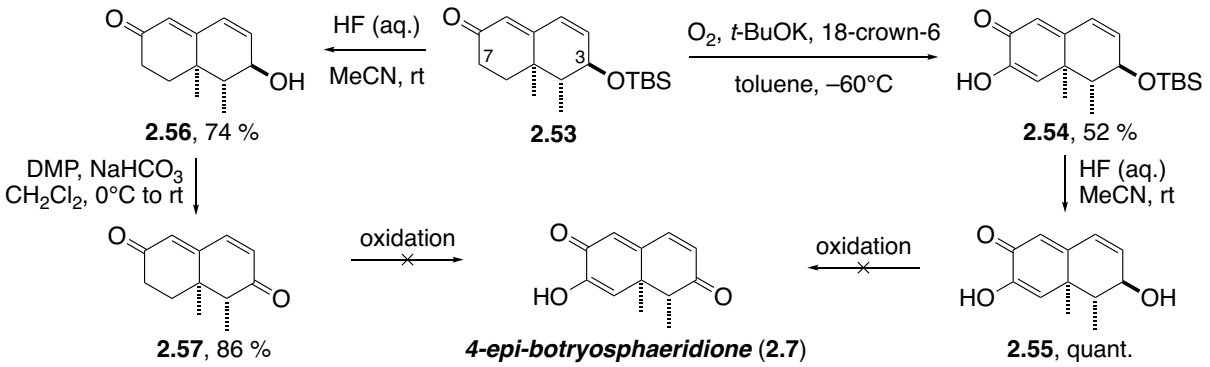
2.2.2 Construction of the C-Ring by a Double Aldol Approach

With the AB-ring system **2.53** in hand, we addressed the construction of the C-ring of periconianone A (**2.1**) in order to complete the tricyclic skeleton. As pointed out in the retrosynthetic analysis (see section 2.1.2) and on closer examination of the proposed biosynthetic pathway, a double aldol reaction would culminate in the desired connectivity (Scheme 2.22). Propanal or an enamine derivative of this aldehyde could first add to a carbonyl group at position C7 of the highly oxidized octalone **2.7**. A second aldol reaction by enolization of the ketone at position C4 and attack to the aldehyde group at C12 could then take place to complete the tricyclic skeleton of periconianone A (**2.1**).



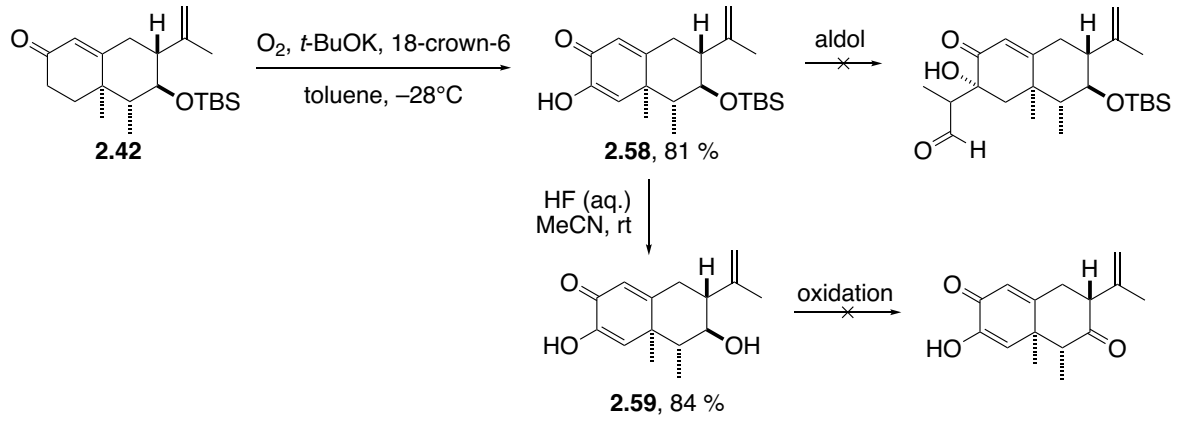
Scheme 2.22: Double aldol approach for the construction of the C-ring of periconianone A (**2.1**).

The first step in this strategy was oxidation of octalone **2.53** at positions C7 and C3 with the goal to synthesize the diosphenol 4-*epi*-botryosphaeridione (**2.6**), a compound isolated from the same extracts as periconianone A.[100] Autoxidation of dienone **2.53** under basic conditions (*t*-BuOK, 18-crown-6, O_2) in toluene at –60°C delivered the α-diketone in 52 % yield (Scheme 2.23). However, ^{1}H NMR analysis ($CDCl_3$) revealed that this compound with the carbonyl group at C7 installed exclusively adopted the enol form to give the diosphenol **2.54**. TBS deprotection using aqueous HF in acetonitrile gave the free allylic alcohol **2.55** in quantitative yield. Unfortunately, attempts to oxidize this hydroxy group were not successful using Dess-Martin periodinane (DMP) and the starting material decomposed during the reaction. Another approach consisted in first modifying the A-ring prior to oxidation at C7: the TBS group of octalone **2.53** was removed in 74 % yield using aqueous HF in acetonitrile to form **2.56**; subsequent oxidation by DMP gave the diene dione **2.57** in 86 % yield but attempts towards the oxidation at position C7 using the conditions elaborated for octalone **2.53** failed and the starting material was decomposed.



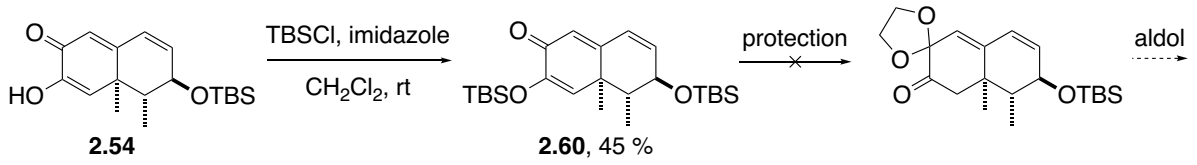
Scheme 2.23: Attempts to synthesize 4-*epi*-botryosphaeridione (**2.7**) as key intermediate in the aldol approach.

In order to study the electrophilicity of the carbonyl group at C7 in light of its preference for the enol form in solution (as observed by ^{1}H NMR spectroscopy), we investigated the primary aldol reaction of our proposal on test substrate **2.58** without modification of the A-ring. Additionally, we planned to test the double aldol approach for the isopropenylated and C3 oxidized diosphenol, planning to remove the three-carbon directing group at C2 at a later stage of the total synthesis. Therefore, the isopropenyl-bearing octalone **2.42** was oxidized using the aforementioned autoxidation conditions to give diosphenol **2.58** in 81 % yield (Scheme 2.24). This reaction had to be carried out at –28°C, as only 38 % of the desired product was formed at room temperature. Unfortunately, no formation of the aldol addition product was observed when reacting diosphenol **2.58** with reagent combinations of propanal and *L*-proline, or with LiHMDS and 1-(prop-1-en-1-yl)piperidine. Modification at the A-ring of **2.58** by deprotection of the TBS group furnished the secondary alcohol **2.59**, but oxidation by DMP only gave a complex mixture.



Scheme 2.24: Formation of diosphenols **2.58** and **2.59** as test substrates in the double aldol approach.

Aiming at an enhancement of the electrophilic character of C7, we investigated a protection strategy for the carbonyl group at C8 as summarized in Scheme 2.25. First the enol with the hydroxy group at C7 was protected as the TBS enol ether **2.60**, after attempts at the formation of the more labile TES enol ether had been hampered by hydrolysis during work-up. Unfortunately, and even though a mild procedure under aprotic conditions was chosen [$(TMSOCH_2)_2$, cat. TMSOTf, 0°C to rt],[135] protection of the C8 carbonyl group as the ketal failed and triggered deprotection of the TBS enol ether instead.



2.54 **2.60**, 45 %

Scheme 2.25: Protection strategy to enhance the electrophilicity of the C7 carbonyl group.

Further studies towards this protection strategy were performed on test substrate **2.61**, after the isopropenyl group of **2.25** had been hydrogenated in the presence of Wilkinson's catalyst.[136] Oxidation to the diosphenol **2.62** proceeded with 77 % yield at –55°C, after no conversion had been observed at lower reaction temperature (–60°C) and formation of a complex mixture at higher temperature (–30°C). However, when **2.62** was heated with ethylene glycol in the presence of a catalytic amount of *p*-TsOH at 110°C in toluene, the desired acetal was not obtained. Instead, formation of a new compound characterized by an aromatic system was observed. Careful structure elucidation using 2D NMR spectroscopy revealed the compound to be catechol **2.63**. Heating either **2.62** or TBS-protected diosphenol **2.64** with *p*-TsOH in toluene at 100°C gave the same compound **2.63**, starting from the latter in 68 % yield. Mechanistically, it is proposed that upon protonation of the C8 carbonyl group, a [1,2]-alkyl shift from C5 to C10 takes place to form the 5,6-spirocyclic intermediate **2.65**, which can subsequently undergo a second [1,2]-alkyl shift from C10 to C9 to form catechol **2.63**. This kind of [1,3]-alkyl migration was first described by A. Andreocci in 1893 in the acid-catalyzed transposition of santonin to desmotroposantonin,[137] and later pioneered and termed dienone-phenol rearrangement by A. L. Wilds and C. Djerassi in 1946.[138] Due to the increased reactivity of the highly oxidized diosphenol, we investigated the reduction of the C8 carbonyl moiety. Reduction with $NaBH_4$ in MeOH gave no conversion, but with the Luche protocol ($NaBH_4$,

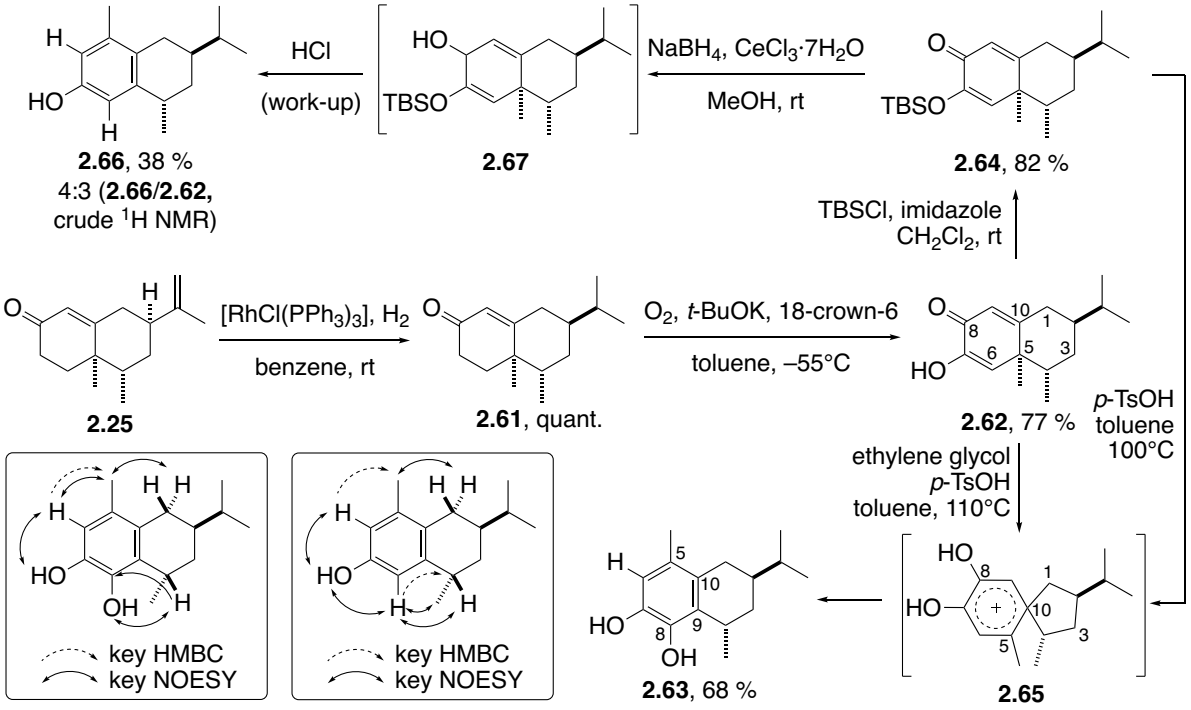
[135] T. Tsunoda, M. Suzuki, R. Noyori, *Tetrahedron Lett.* **1980**, *21*, 1357-1358.

[136] J. A. Osborn, F. H. Jardine, J. F. Young, G. Wilkinson, *J. Chem. Soc. A* **1966**, 1711-1732.

[137] A. Andreocci, *Gazz. Chim. Ital.* **1893**, *23*, 468-476.

[138] A. L. Wilds, C. Djerassi, *J. Am. Chem. Soc.* **1946**, *68*, 1715-1719.

$CeCl_3 \cdot 7H_2O$, MeOH, rt) followed by acidic work-up, phenol **2.66** and deprotected diosphenol **2.62** were formed in a 4:3 ratio, as monitored by ^{1}H NMR spectroscopy of the crude reaction mixture. This kind of reduction and rearrangement cascade has been described by H. Dannenberg *et al.* on oxidized testosterone derivatives:[139] reduction of the carbonyl moiety forms the intermediate **2.67**, which dehydrates upon protonation of the hydroxy group and rearranges to the phenol **2.66** in a dienol-phenol rearrangement. Unfortunately, this experiment was not reproducible and no reduction took place when protected diosphenol **2.64** was subjected to the same reaction conditions.



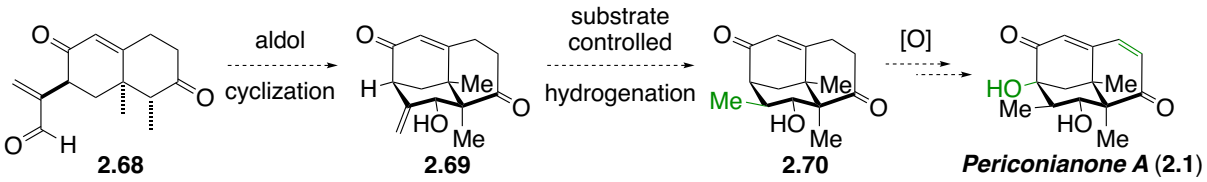
Scheme 2.26: Investigations for protection or reduction of the C8 carbonyl group using the test substrate **2.61**.

Starting from octalone **2.25**, we also tested a sequence featuring C7-hydroxylation, protection of the C8 carbonyl group and oxidation of the newly installed C7 hydroxy substituent to the ketone. Oxidation in α-position of the carbonyl group in octalone **2.25** was either performed by Rubottom oxidation or treatment with $Pb(OAc)_4$ to afford the C7–*O*-acetylated compound. However, protection of the C8 carbonyl group did neither take place for the C7–OH nor the C7–OAc octalones. Due to the increased reactivity of the highly oxidized diosphenols, their potential role as intermediates in this synthesis was not investigated any further.

[139] H. Dannenberg, D. Dannenberg-von Dresler, T. Köhler, *Chem. Ber.* **1960**, *93*, 1989-1998.

2.2.3 Late Stage C7 Hydroxylation Approach

In the presented approach summarized in Scheme 2.27, we envisioned the construction of the tricyclic skeleton in a stepwise procedure by installation of a side chain at C7 as a first step in order to obtain the tricarbonyl intermedate **2.68**. Aldol cyclization would then form the 6/6/6 tricarbocyclic skeleton **2.69**, whose terminal olefin at C11=C13 could be reduced in a stereoselective substrate-controlled hydrogenation from the convex side of the molecule by coordination of the catalyst's transition metal ion to the hydroxy group at C12. Dehydrogenation of the C1–C2 bond of **2.70** as well as oxidation at C7 would form periconianone A (**2.1**).



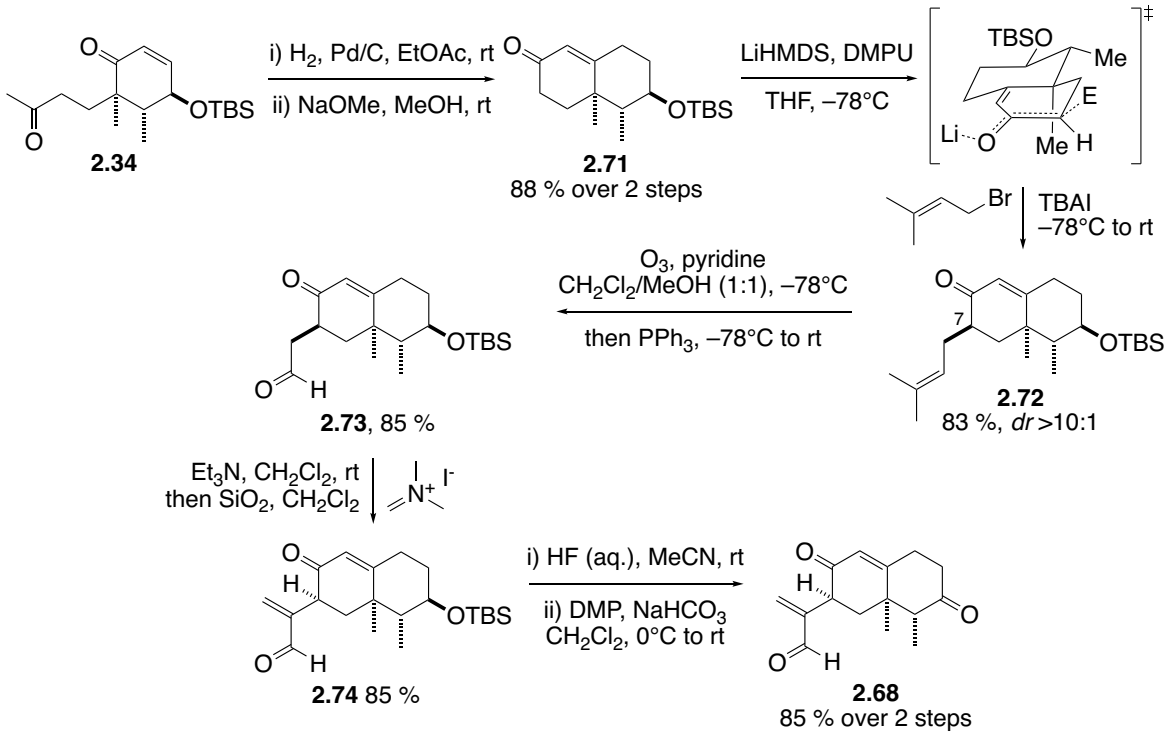
Scheme 2.27: Tricarbonyl compound **2.68** as an intermediate for the synthesis of periconianone A (**2.1**) by aldol cyclization, substrate-controlled hydrogenation of the terminal methylene group and late-stage dehydrogenation (C1–C2) and hydroxylation (C7).

2.2.3.1 Installation of the α,β-Unsaturated Aldehyde Side Chain at C7

After bicyclic dienone **2.53** had been shown to be too reactive in the ensuing steps of the synthesis and mainly decomposed in the C7 alkylation process, we decided to remove the unsaturation in the monocyclic enone **2.34**. Hydrogenation using Pd/C as catalyst in ethyl acetate (Scheme 2.28) gave the diketone intermediate. On the other hand, with methanol as solvent a mixture of desired ketone and the corresponding dimethyl acetal was formed. Similar observations for the reduction of a bicyclic enone in the presence of methanol are described by P. Hudson and P. J. Parson.[140] Subsequently, the B-ring was formed by an aldol condensation reaction using NaOMe in methanol at room temperature to furnish the desired octalone **2.71** in 88 % yield over two steps. Allylation of octalone **2.71** at position C7 was low-yielding (LDA, allyl bromide, DMPU, THF, –78°C to rt, o.n.): the reaction stopped at around 50 % conversion with only 30 % isolated yield. Increasing the number of equivalents of base or of allyl bromide did not have any influence on the conversion; instead double allylation at position C7 was observed. Therefore, we introduced the less reactive prenyl group, not only to avoid dialkylation, but also for its higher reactivity in the subsequent ozonolysis step, as the prenyl group's double bond is more electron-rich compared to the one of the allyl group. Treatment of

[140] P. Hudson, P. J. Parsons, *Synlett* **1992**, 867-868.

octalone **2.71** with LiHMDS in THF/DMPU at –78°C was followed by addition of TBAI and prenyl bromide. The mixture was slowly warmed up to room temperature and stirred overnight. The desired prenylated octalone **2.72** was isolated with 83 % yield in a diastereomeric ratio of >10:1 in favor of the desired 7*R*-configured stereoisomer. The stereochemical outcome of this diastereoface-differentiating addition on the enolate is explained by the transition state shown in Scheme 2.28: all substituents in the A-ring are in an equatorial orientation except for the angular methyl group at C5, which shields the *Si* face and thus favors electrophilic attack on the α carbon atom from the *Re* face.



Scheme 2.28: Formation of octalone **2.71** and installation of the C7 side chain.

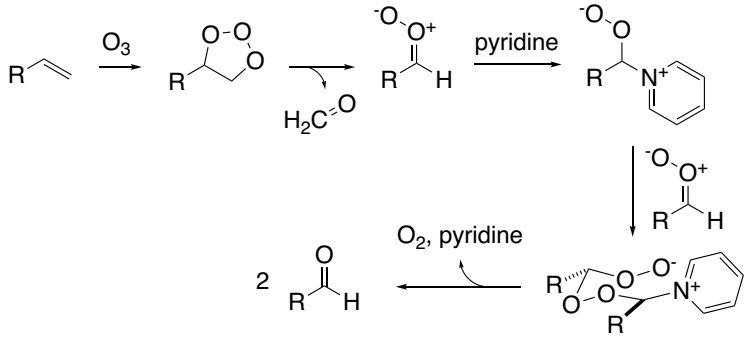
Ozonolysis was performed in a mixture of CH_2Cl_2 and MeOH using pyridine as a co-solvent. Pyridine is known to increase the yield for various substrates in the ozonolysis reaction[141] and allows for better regioselectivity.[142] More recently, the function of pyridine was examined more closely and the mechanism of this transformation has been studied by the group of P. H. Dussault (Scheme 2.29).[143] They propose pyridine to be an organocatalyst in the reaction, *viz.* after the primary ozonide is broken up, addition of pyridine to the carbonyl oxide

[141] K. Griesbaum, *Chem. Commun. (London)* **1966**, 920-921; G. Slomp, J. L. Johnson, *J. Am. Chem. Soc.* **1958**, *80*, 915-921.

[142] E. J. Corey, K. Achiwa, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1969**, *91*, 4318-4320; B. M. Trost, M. R. Machacek, H. C. Tsui, *J. Am. Chem. Soc.* **2005**, *127*, 7014-7024.

[143] R. Willand-Charnley, T. J. Fisher, B. M. Johnson, P. H. Dussault, *Org. Lett.* **2012**, *14*, 2242-2245.

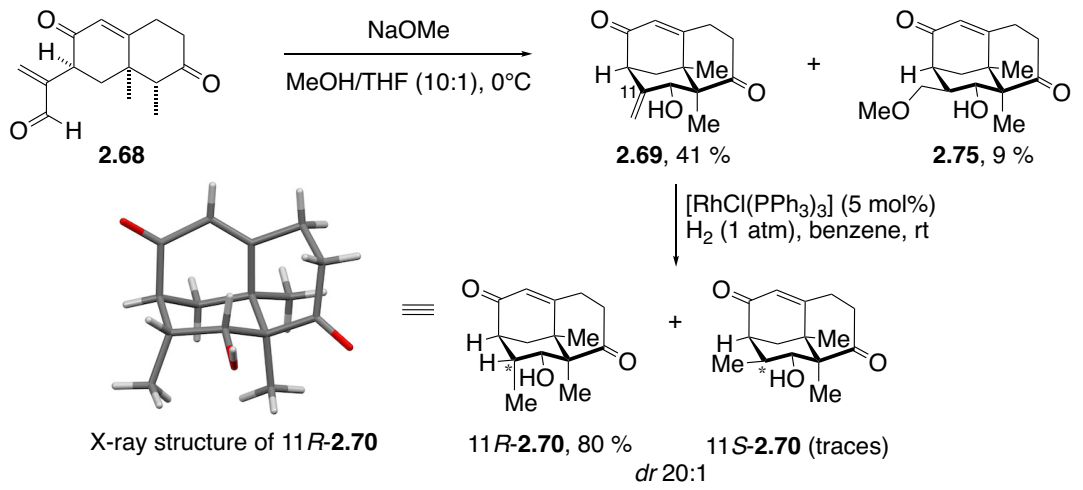
can take place to generate a zwitterion that might react with another carbonyl oxide. The formed bisperoxyacetal then undergoes fragmentation to form molecular oxygen, two carbonyl groups, and release pyridine. Using the conditions given in Scheme 2.28, we isolated 85 % of aldehyde **2.73**. When the reaction was performed in the absence of pyridine, a complex mixture was formed containing traces of the desired compound. The methylene group was installed under basic conditions using Eschenmoser's salt (dimethylmethylideneammonium iodide) and the desired enal **2.74** was formed in 85 % yield. After removal of the TBS group by treatment with aqueous HF in acetonitrile and oxidation by DMP, tricarbonyl **2.68** was isolated in 85 % yield over two steps.



Scheme 2.29: Mechanism for ozonolysis in the presence of pyridine as proposed by the group of P. H. Dussault.

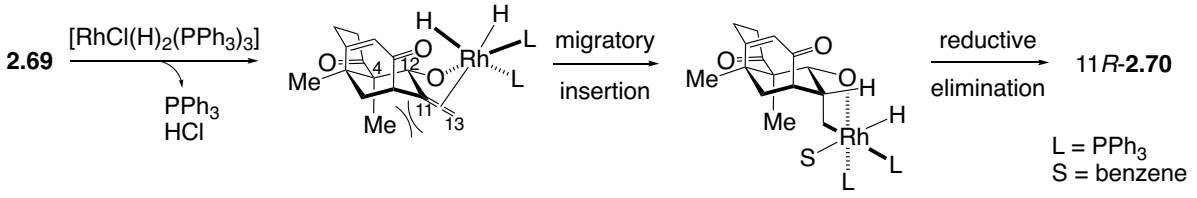
2.2.3.2 Aldol Cyclization of α,β-Unsaturated Aldehyde 2.68

With tricarbonyl compound **2.68** in hand, the stage was set to investigate the key aldol transformation of the presented synthetic route. This reaction was found to work best with NaOMe in a 10:1 MeOH/THF mixture at 0°C. The desired tricyclic compound **2.69** was isolated in 41 % and methyl ether **2.75** in 9 % yield. The latter compound is presumably formed upon Michael addition of methoxide to the enal, which can then undergo the aldol addition process. With K_2CO_3 as a base in the same solvent mixture, only 25 % yield of the desired aldol addition product **2.69** was achieved. Using DBU in toluene at room temperature resulted in formation of a complex mixture, whereas no conversion was observed with titanium tetrachloride in toluene.



Scheme 2.30: Aldol cyclization of α,β-unsaturated aldehyde **2.68** and hydrogenation attempt.

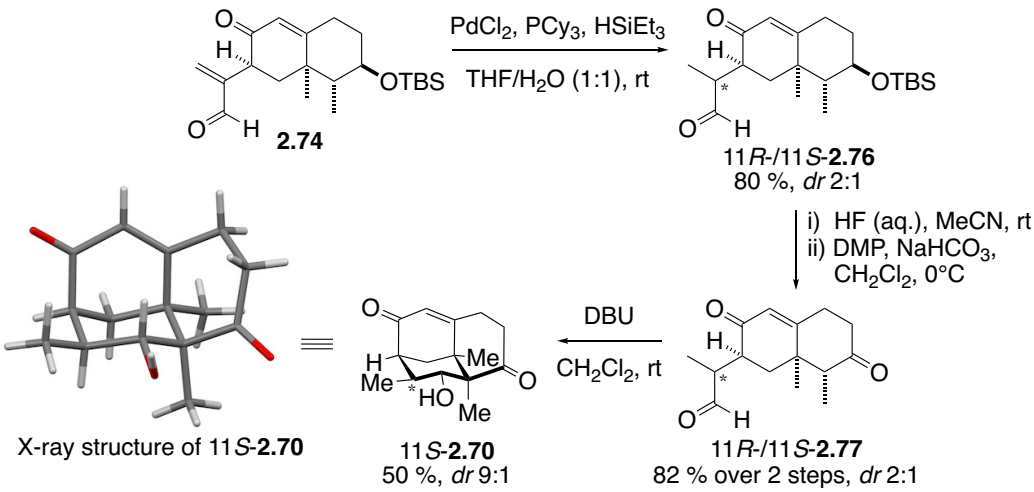
For the ensuing steps of the synthesis, we planned to first hydrogenate the terminal double bond, followed by two oxidation steps to deliver periconianone A (**2.1**). The hydrogenation was supposed to proceed diastereoface-selectively from the convex *Re* face of **2.69**. However, the reaction with Wilkinson's catalyst (benzene, rt, 1 atm of H_2) almost exclusively proceeded by *Si* face attack on the double bond, thus forming the undesired 11*R*-stereoisomer **2.70** in 80 % yield with a diastereomeric ratio of 20:1. The structure of the product stereoisomer was confirmed by single-crystal X-ray analysis. The first step in the hydrogenation with Wilkinson's complex is oxidative *cis*-addition of H_2 on the pre-catalyst $[RhCl(PPh_3)_3]$ to give the fully saturated Rh(III) complex $[RhCl(H)_2(PPh_3)_3]$. Ligand substitution of the chloride by the alkoxide on C12 and of one phosphine ligand by π-coordination of the terminal alkene of **2.69** gives the intermediate complex shown in Scheme 2.31 (L = PPh_3). Migratory insertion is the rate-determining step leading to an intermediate featuring a 5,6-*cis* fused ring system, where S is a solvent molecule (benzene) coordinating to the central Rh(III) ion (Scheme 2.31). The stereoselectivity of this hydrogenation is determined by the face, from which the hydrogen atom is transferred, *i.e.* either from the *Si* or from the *Re* face of the terminal double bond. We propose that the observed formation of the 11*R*-stereoisomer is favored due to steric hindrance by the methyl group at C4, thus blocking the *Re* face of the terminal double bond for coordination of Wilkinson's catalyst.



Scheme 2.31: Proposed mechanism in the Rh-catalyzed hydrogenation leading to the 11*R*-isomer of tricycle **2.70** (S = solvent molecule).

2.2.3.3 Enal Reduction and Aldol Cyclization of α-Methylated Aldehyde 2.76

Aiming to prepare tricycle **2.70** with 11*S*-configuration, we investigated an alternative route by installing the methyl group at C11 earlier in the synthesis. After attempts at the methylation of C11 on aldehyde **2.73** or its dimethyl hydrazone derivative had turned out unsuccessful, we elaborated a protocol for the reduction of enal **2.74**. We were aware of the formation of a diastereomeric mixture with *R*- and *S*-configuration at C11; however, we presumed that the aldol addition under basic conditions would be fully reversible and epimerization of the stereogenic center at the α-position to the aldehyde group would finally lead to the thermodynamically more favorable diastereoisomer with the methyl group in the equatorial position (see structure **2.70**, Scheme 2.32). Although using high catalyst loadings and 1 to 10 atm of H_2 pressure, hydrogenation experiments in the presence of Pd/C or Wilkinson's catalyst were very low-yielding. Additionally, Wilkinsons's catalyst triggered decarbonylation of the aldehyde.[144] Therefore, we screened different protocols for 1,4-hydrosilylation and subsequent hydrolysis of the intermediary silyl enol ether. Best results in terms of yield and chemoselectivity were obtained with palladium nanoparticles.[145]



Scheme 2.32: Enal reduction approach and aldol cyclization of α-methylated aldehyde **2.76**.

A heterogeneous mixture of substrate **2.74**, $HSiEt_3$, $PdCl_2$ and tricyclohexylphosphine (PCy_3) in THF/water (1:1) was stirred at room temperature and formed the desired methylated

[144] J. Tsuji, K. Ohno, *Tetrahedron Lett.* **1965**, *6*, 3969-3971; K. Ohno, J. Tsuji, *J. Am. Chem. Soc.* **1968**, *90*, 99-107.

[145] M. Benohoud, S. Tuokko, P. M. Pihko, *Chem. Eur. J.* **2011**, *17*, 8404-8413.

aldehyde **2.76** in 80 % yield and a diastereomeric ratio of 2:1. When the reaction was performed in the absence of water, formation of a mixture of desired aldehyde **2.76** and its silyl enol ether was observed. For analytical purposes, the diastereoisomers were separated. By aldol cyclization of diastereopure 11*R*- and 11*S*-**2.77** to **2.70** under conditions that prevent isomerization of the stereogenic center at C11 (diphenyl phosphate, toluene, 65°C; see section 2.2.6.2) and analysis of the corresponding crude ^{1}H NMR spectra, we revealed that the 11*R*-configured diastereoisomer was preferably formed in the enal reduction.

Modification of the A-ring by deprotection of the TBS group and oxidation of the secondary alcohol to the ketone set the stage for the aldol reaction. Applying the conditions used for the transformation of enal **2.68** to **2.69** (NaOMe in MeOH/THF at 0°C) gave only traces of the desired product after stirring for three hours, and a complex mixture when stirred overnight. However, performing the reaction at a temperature between 15 and 25°C formed tricycles 11*R*-**2.70** and 11*S*-**2.70** in 33 % yield and a diastereomeric ratio of 4:1. When the 11*R*-isomer of aldehyde **2.77** was used as starting material for this reaction, the ^{1}H NMR spectrum of the crude product indicated epimerization at C11: both the 11*S*-isomer of the starting material **2.77** as well as the desired *S*-configured tricycle **2.70** were detected. Screening for improved reaction conditions, we found even more side product formation using the inorganic base K_2CO_3 in MeOH at room temperature. An improved yield of 50 % of tricycle **2.70** in a diastereomeric ratio of 9:1 (11*S*/11*R*) was obtained using the amidine base DBU in CH_2Cl_2 at room temperature.[146] After crystallization, the structure of tricycle 11*S*-**2.70** was confirmed by single-crystal X-ray analysis.

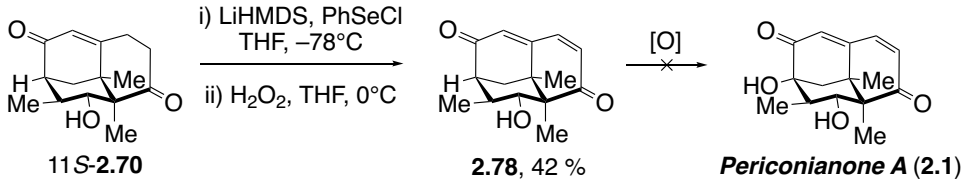
2.2.3.4 Dehydrogenation of the C1–C2 Bond and C7 Hydroxylation Attempts

With tricycle 11*S*-**2.70** in hand and in order to complete the total synthesis of periconianone A (**2.1**), we envisioned to first dehydrogenate the C1–C2 carbon bond in the A-ring, followed by installation of the C7 hydroxy group. Deprotonation at C2 by LiHMDS and trapping of the formed enolate as TMS enol ether was performed quantitatively. However, Saegusa oxidation ($Pd(OAc)_2$, MeCN, rt)[112,147] of the TMS enol ether was very low-yielding and only traces of the desired product were detected in the ^{1}H NMR spectrum of the crude mixture. With the one-step protocol using the reagent combination of IBX and MPO in DMSO, no conversion was observed, not even at 80°C.[113] Unfortunately, the same result was obtained

[146] C. Li, X. Yu, X. Lei, *Org. Lett.* **2010**, *12*, 4284-4287; I. Cota, R. Chimentao, J. Sueiras, F. Medina, *Catal. Commun.* **2008**, *9*, 2090-2094.

[147] S. B. Herzon, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 5342-5344.

by using iodic acid in a DMSO/cyclohexane mixture (5:1).[148] The desired diene dione **2.78** was finally produced in 42 % yield by selenoxide elimination: α-selenylation using LiHMDS and phenylselenyl chloride in THF at –78°C was followed by oxidation with hydrogen peroxide at 0°C (Scheme 2.33).[111]



Scheme 2.33: Dehydrogenation and attempted C7 hydroxylation.

Numerous studies have been reported for the α-hydroxylation of carbonyl compounds, typically involving oxidation of the corresponding enolates or silyl enol ethers by hypervalent iodine compounds[149] or oxygen transfer reagents, such as metal oxidants[150] [*i.e.* MoO_5·pyridine·HMPA, $Pb(OAc)_4$, $Tl(OAc)_3$, OsO_4], *N*-sulfonyl oxaziridines,[151] dioxiranes[152] and perbenzoic acids[153] (Rubottom oxidation). Sir D. H. R. Barton and co-workers reported autoxidation of pregnan-20-one using sodium or potassium alkoxides and molecular oxygen.[154] The formed α-hydroxyperoxy ketone intermediates can then be reduced in the presence of zinc and acetic acid. Later, the group of J. N. Gardner found superior yields for this process by using the reductant triethyl phosphite for quenching the intermediary hydroperoxy radicals *in situ*, thus avoiding side reactions like oxidative α-carbon cleavage due to the presence of reactive radical species.[155] Unfortunately, applying the described conditions to tricycle **2.78** using *t*-BuOK and $P(OMe)_3$ in a THF/*t*-BuOH mixture (4:1) under an O_2 atmosphere at –40°C only gave a complex mixture. No conversion was observed when replacing the alkoxide with Cs_2CO_3 as base and the solvent mixture with DMSO, as described in a recently reported

[148] K. C. Nicolaou, T. Montagnon, P. S. Baran, *Angew. Chem. Int. Ed.* **2002**, *41*, 1386-1389.

[149] A. Duschek, S. F. Kirsch, *Chem. Eur. J.* **2009**, *15*, 10713-10717; R. M. Moriarty, S. C. Gupta, H. Hu, D. R. Berenschot, K. B. White, *J. Am. Chem. Soc.* **1981**, *103*, 686-688.

[150] G. M. Rubottom, R. Marrero, J. M. Gruber, *Tetrahedron* **1983**, *39*, 861-865; J. P. McCormick, W. Tomasik, M. W. Johnson, *Tetrahedron Lett.* **1981**, *22*, 607-610; A. McKillop, J. D. Hunt, E. C. Taylor, *J. Org. Chem.* **1972**, *37*, 3381-3382; E. Vedejs, D. A. Engler, J. E. Telschow, *J. Org. Chem.* **1978**, *43*, 188-196.

[151] F. A. Davis, B. C. Chen, *Chem. Rev.* **1992**, *92*, 919-934.

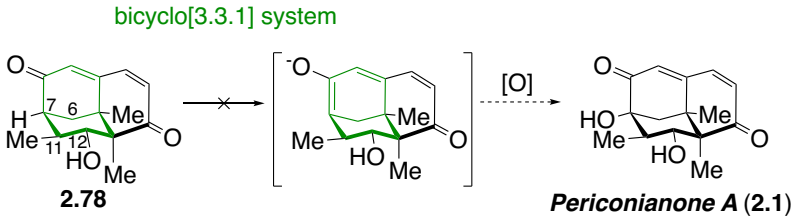
[152] W. Adam, L. Hadjiarapoglou, X. Wang, *Tetrahedron Lett.* **1989**, *30*, 6497-6500.

[153] G. M. Rubottom, R. Marrero, *J. Org. Chem.* **1975**, *40*, 3783-3784; G. M. Rubottom, R. Marrero, *Synth. Commun.* **1981**, *11*, 505-511.

[154] E. J. Bailey, D. H. R. Barton, J. Elks, J. F. Templeton, *J. Chem. Soc.* **1962**, 1578-1591.

[155] J. N. Gardner, T. L. Popper, F. E. Carlon, O. Gnoj, H. L. Herzog, *J. Org. Chem.* **1968**, *33*, 3695-3699; J. N. Gardner, F. E. Carlon, O. Gnoj, *J. Org. Chem.* **1968**, *33*, 3294-3297.

protocol for the formation of various tertiary α-hydroxy ketones.[156] Before screening of reaction conditions was continued, we tested the accessibility of C7–H towards deprotonation. Deuteration experiments by quenching a reaction mixture of **2.78** and base (LDA/LiHMDS/KHMDS/NaHMDS/*t*-BuOK) at different temperatures from –78°C to 0°C with CD_3OD revealed this bridgehead position not to be accessible for deprotonation. The qualitative generalization describing the structural limitation of reactivity in bridged ring compounds is known as Bredt's rule:[157] except for larger ring systems, compounds with a C=C or C=N double bond at a branching position of a carbon bridge ("bridgehead") cannot exist due to the lack of π overlap as a result of the steric constraints that impede the required alignment of the p_z orbitals. However, limits for the validity of Bred's rule have been described by V. Prelog *et al.*[158] and many other research groups.[159] A more quantitative definition for the limits of Bredt's rule was later defined by F. S. Fawcett, who introduced the *S* value as the sum of the number of atoms in the bridges of a polycyclic system.[160] Bicyclic compounds with an *S* value of ≥ 9 were categorized as isolable with a bridgehead double bond and those with a *S* value of ≥ 7 as observable. However, the synthesis of isolable bicylco[3.3.1]non-1-ene by J. R. Wiseman[161] and J. A. Marshall[162] and subsequent studies on highly strained bicyclic alkenes called for a revision of this rule. Tricyclic rings have been discussed as well, but due to their complexity, one of the three carbocycles is usually neglected and the system analyzed as if it were a bicycle.[160] Thus, in the case of tricyclic **2.78**, the BC-ring system might be specified as a bicyclo[3.3.1] core (Scheme 2.34).



Scheme 2.34: Deprotonation attempts on tricyclic compound **2.78**.

[156] Y.-F. Liang, N. Jiao, *Angew. Chem. Int. Ed.* **2014**, *53*, 548-552.

[157] J. Bredt, *Liebigs Ann. Chem.* **1924**, *437*, 1-13.

[158] V. Prelog, P. Barman, M. Zimmermann, *Helv. Chim. Acta* **1949**, *32*, 1284-1296; V. Prelog, *J. Chem. Soc.* **1950**, 420-428.

[159] K. J. Shea, *Tetrahedron* **1980**, *36*, 1683-1715.

[160] F. S. Fawcett, *Chem. Rev.* **1950**, *47*, 219-274.

[161] J. R. Wiseman, *J. Am. Chem. Soc.* **1967**, *89*, 5966-5968.

[162] J. A. Marshall, H. Faubl, *J. Am. Chem. Soc.* **1967**, *89*, 5965-5966.

More recent studies on bridgehead lithiation – substitution studies on bicyclic [3.3.1] ketones have shown the feasibility of bridgehead enolization in those systems.[163] However, we suppose that the additional fused A-ring of **2.78** as well as the conjugated diene dione moiety strongly influence the geometry and contribute to higher ring strain in the BC-ring system. Extensive research in the field of C–H activation led to protocols addressing chemo-, regio- and stereoselective oxidation.[164] However, neither the structural features of the catalyst nor the presence of directing groups in the starting material have any systematic influence on the selectivity and outcome of the reactions. A general trend for oxidizability is observed with regard to the electronic and steric properties of the C–H bonds: most of the known reagents for C–H activation are electrophilic and prefer oxidation of electron-rich as well as sterically less hindered bonds. For ring systems, another general observation has been reported, *viz.* faster activation of equatorial C–H bonds compared to axial ones regardless of the choice of reagent system. K. Chen, A. Eschenmoser and P. Baran explain this phenomenon to be mainly based on strain release during the transition to the activated complex, which is larger for equatorial C–H bonds than for axial ones.[165] However, in the case of **2.78**, electronic considerations are conflictive with those based on strain release arguments: comparing the chemical shifts of the ^{13}C NMR signals of tricycle **2.78** as an indicator of the corresponding C–H bond's electron density, the signals for C6 (37.1 ppm) and C11 (33.2 ppm) are more upfield compared to C7 (48.9 ppm), thus hinting at the tendency of positions C6 and C11 to be oxidized prior to position C7 based on electronic reasoning, whereas position C7 is expected to be oxidized more readily based on strain release arguments. In face of these opposing arguments, we tested the reactivity of tricycle **2.78** towards the White-Chen catalyst (Fe(PDP), AcOH, H_2O_2, MeCN, rt).[164c] Unfortunately, the ^{1}H NMR spectrum of the crude reaction mixture showed decomposition of the starting material and formation of a complex mixture. The same results were obtained by applying stable radical cation salts derived from triarylamines [tris(4-bromophenyl)ammoniumyl hexachloroantimonate, K_2CO_3, MeCN/H_2O, rt], which are known to oxidize ketones to the corresponding α-hydroxy ketones or α-diketo compounds.[166] In order to test additional conditions, one might consider protection of the C12–OH group, which is

[163] C. J. Hayes, N. S. Simpkins, D. T. Kirk, L. Mitchell, J. Baudoux, A. J. Blake, C. Wilson, *J. Am. Chem. Soc.* **2009**, *131*, 8196-8210.

[164] M. Canta, M. Rodríguez, M. Costas, in Site-Selective Catalysis (Ed.: T. Kawabata), Springer International Publishing, Cham, **2015**, pp. 27-54; T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 3362-3374; M. S. Chen, M. C. White, *Science* **2007**, *318*, 783-787; G. J. Chuang, W. Wang, E. Lee, T. Ritter, *J. Am. Chem. Soc.* **2011**, *133*, 1760-1762; L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542-9543.

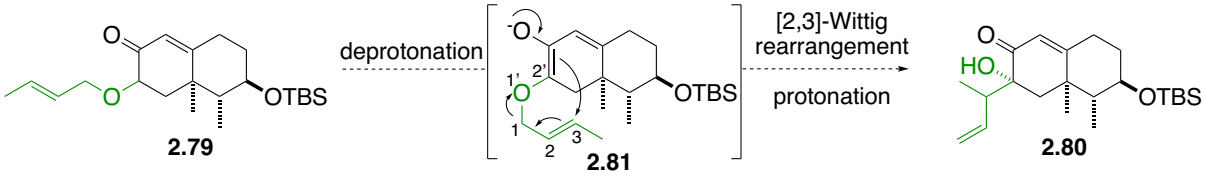
[165] K. Chen, A. Eschenmoser, P. S. Baran, *Angew. Chem. Int. Ed.* **2009**, *48*, 9705-9708.

[166] M. Schulz, R. Kluge, L. Sivilai, B. Kamm, *Tetrahedron* **1990**, *46*, 2371-2380.

prone to oxidize to the ketone under the given reaction conditions. However, taking into account the highly reactive nature of the diene dione system, we finally had to abandon this approach and install the tertiary carbinol at an earlier stage of the synthesis.

2.2.4 [2,3]-Wittig Rearrangement Approach

This approach was designed in order to facilitate an early installation of the tertiary carbinol at the stage of the bicyclic AB-ring system. It was envisioned to first synthesize the C7 crotyl ether **2.79**, which would undergo a [2,3]-sigmatropic rearrangement upon deprotonation of the C7–H to form the desired C7 carbinol **2.80** (Scheme 2.35). As one of the best investigated variants of a [2,3]-shift, this kind of transformation involving α-oxy carbanions is better known as the [2,3]-Wittig rearrangement. This [2,3]-shift works best when the intermediary carbanion is stabilized by an electron-withdrawing group, as in intermediate **2.81**. However, although various "π-acceptor" functional groups are reported for their beneficial effect on Wittig [2,3]-shifts, examples with carbanions/enolates derived from α-allyloxy carbonyl compounds are rare, as they can undergo either the [2,3]-shift or the competing [3,3]-sigmatropic rearrangement, depending on the reaction conditions.[167]



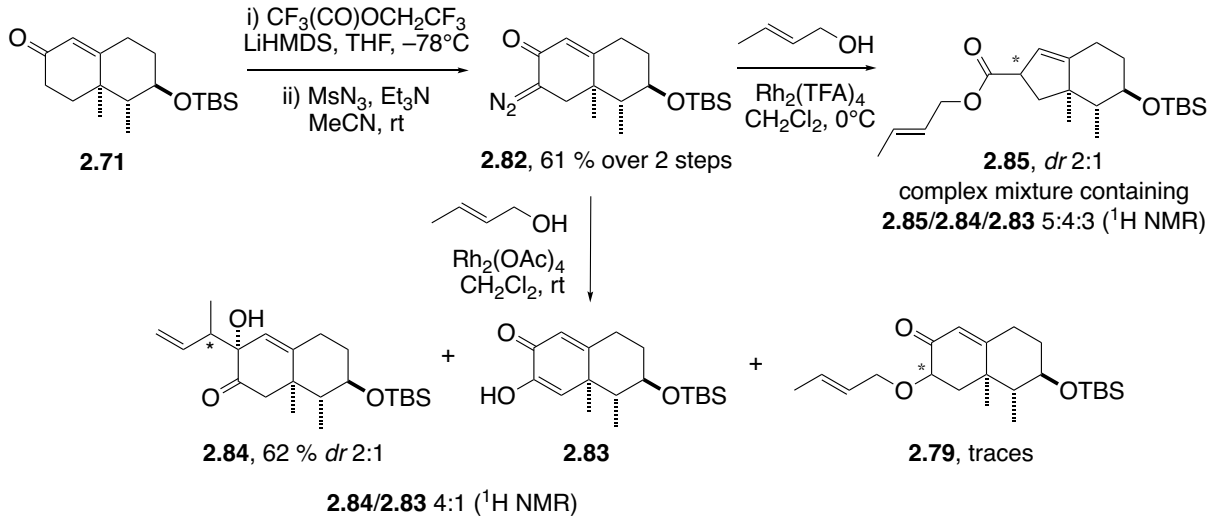
Scheme 2.35: [2,3]-Wittig rearrangement approach for the stereoselective installation of the C7 carbinol.

For the synthesis of crotylated α-hydroxyenone **2.79**, we intended to synthesize α-diazoketone **2.82**, which would undergo an O–H insertion using crotyl alcohol in the presence of a Rh(II)-catalyst. Direct diazoketone formation under basic conditions was unsuccessful and resulted in formation of a complex mixture. Therefore, we used a two-step protocol: the enolate of octalone **2.71** was quantitatively converted to the trifluoroacylated compound using trifluoroethyl trifluoroacetate at –78°C. Treatment of this compound with mesyl azide and triethylamine gave the desired diazoketone **2.82** in 61 % yield over two steps (Scheme 2.36).[168] The yield of our initial experiments was around 22 to 28 %, and we found that slow addition of the mesyl azide by syringe pump and prolonged reaction time significantly increased formation

[167] J. Kallermerten, in Houben-Weyl, Methods of Organic Chemistry, *Vol. E 21d* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme Verlag, Stuttgart, **1995**, pp. 3757-3809.

[168] R. L. Danheiser, R. F. Miller, R. G. Brisbois, S. Z. Park, *J. Org. Chem.* **1990**, *55*, 1959-1964.

of the desired diazoketone **2.82**. Unfortunately, the reaction of **2.82** with *trans*-crotyl alcohol in the presence of Rh(II) did not form the anticipated ether **2.79** as the primary insertion product. Slow addition of a solution of diazoketone **2.82** in CH_2Cl_2 to a solution of four equivalents of *trans*-crotyl alcohol and 1 mol% $Rh_2(OAc)_4$ in CH_2Cl_2 mainly yielded diosphenol **2.83**. Increasing the number of equivalents for *trans*-crotyl alcohol (20 equiv.) led to formation of α-allylated α-hydroxyketone **2.84** and diosphenol **2.83** in a 4:1 mixture, of which **2.84** was isolated in 62 % yield as a diastereomeric mixture (2:1) after column chromatography. More details and mechanistic discussion for this transformation will be given in section 2.2.6. Using $Rh_2(TFA)_4$ as catalyst, a complex mixture was formed containing α-allylated α-hydroxyketone **2.84**, diosphenol **2.83** and a third compound (**2.85**) in a ratio of 4:3:5. The unknown compound was identified as the ring contraction product **2.85** upon isolation and structural elucidation by 2D NMR spectroscopy.

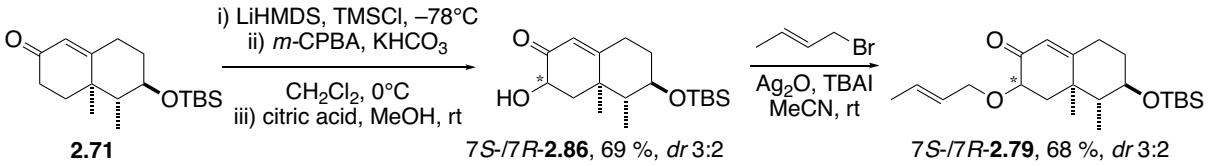


Scheme 2.36: Synthesis of α-diazoketone **2.82** and attempted OH-insertion reaction.

Aiming to prepare α-keto ether **2.79**, we started to investigate an alternative route involving α-hydroxylation of octalone **2.71** followed by *O*-crotylation. Installation of the hydroxy group was achieved using the Rubottom protocol:[169] the silyl enol ether was formed by treatment of octalone **2.71** with LiHMDS and TMSCl at –78°. Treatment with *m*-CPBA and work-up was followed by stirring the crude mixture containing the desired α-hydroxy ketone and the partially silylated α-hydroxy ketone with citric acid in MeOH to give α-hydroxy ketone **2.86** in 69 % yield and a diastereomeric ratio of 3:2 (7*S*/7*R*). For analytical purposes, the diastereoisomers were separated and their absolute configuration was established using

[169] A. Hassner, R. H. Reuss, H. W. Pinnick, *J. Org. Chem.* **1975**, *40*, 3427-3429; G. M. Rubottom, M. A. Vazquez, D. R. Pelegrina, *Tetrahedron Lett.* **1974**, *15*, 4319-4322.

NOESY NMR spectroscopy. The diastereomeric mixture of **2.86** was submitted to crotylation using Ag_2O, TBAI and crotyl bromide to give crotylated α-hydroxy enone **2.79** in 68 % yield and retained diastereomeric ratio of 3:2 (7*S*/7*R*, Scheme 2.37). In the absence of TBAI, the reaction was slower and had to be heated to 45°C to observe conversion. This modification resulted in lower yields due to increased side product formation. Using sodium hydride as base in THF at 0°C to room temperature as well as *n*-BuLi at –78°C only led to formation of a complex mixture.



Scheme 2.37: Rubottom oxidation of octalone **2.71** followed by *O*-crotylation.

With crotylated α-hydroxy enone **2.79** in hand, we started to investigate the feasibility of the [2,3]-Wittig rearrangement and screened reaction conditions, as summarized in Table 2.3. At low temperature (–70°C), lithium enolates derived from ketones or esters generated in HMPA-THF are reported to selectively undergo the [2,3]-shift, and not the [3,3]-Claisen rearrangement.[170] Unfortunately, neither at –78°C (entry 1) nor by gradually warming up the reaction mixture (entry 2) could we detect formation of the desired rearranged product. Lewis base catalysts have been reported to induce [2,3]-Wittig rearrangements of silyl enol ethers generated from the corresponding α-allyloxy carbonyl compounds.[171] The corresponding TMS enol ether of **2.79** was formed quantitatively by treatment with TMSOTf and Et_3N in CH_2Cl_2. Unfortunately, treatment of crude TMS enol ether with LiHMDS did not induce the desired [2,3]-shift (entry 3). S. E. Denmark and co-workers have recently reported a quaternary ammonium phase-transfer catalyzed [2,3]-Wittig rearrangement for a very limited substrate scope.[172] Applying their reaction conditions (entry 4), we were not able to observe any conversion and a diastereoisomer of the starting material with epimerization at stereogenic center C7 was recovered. Using tetrabutylammonium hydroxide[173] as phase-transfer catalyst only led to formation of a complex mixture (entry 5). Neither did pyrrolidine as

[170] M. Koreeda, J. I. Luengo, *J. Am. Chem. Soc.* **1985**, *107*, 5572-5573; T. Osamu, S. Takahiro, M. Koichi, N. Takeshi, *Chem. Lett.* **1986**, *15*, 1599-1602.

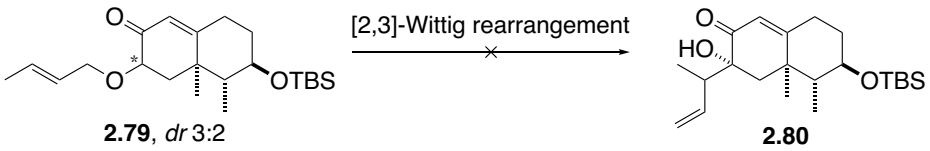
[171] Y. Sato, H. Fujisawa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1275-1287.

[172] S. E. Denmark, L. R. Cullen, *J. Org. Chem.* **2015**, *80*, 11818-11848.

[173] M. J. Jansma, T. R. Hoye, *Org. Lett.* **2012**, *14*, 4738-4741.

organocatalyst[174] bring about the conversion to the desired [2,3]-Wittig rearranged product and formation of a complex mixture was observed by ^{1}H NMR spectroscopy (entry 6).

Table 2.3: Selected conditions for the attempted [2,3]-Wittig rearrangement of α-keto ether **2.79**.

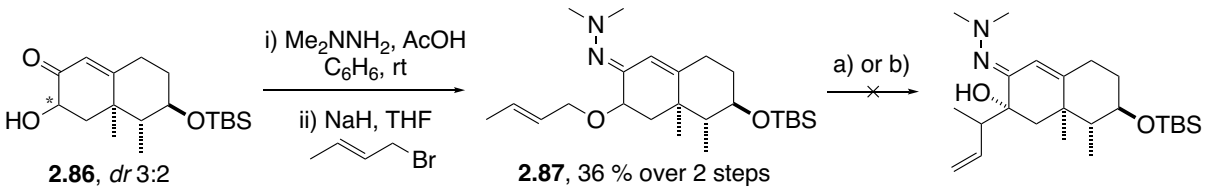


2.79, *dr* 3:2 **2.80**

entry	reagent	solvent	temperature	observations[a]
1	LDA	HMPA/THF	–78°C	low conversion to dealkylated side-product
2	LDA	HMPA/THF	–78°C to –60°C to –20°C to 0°C to rt	complex and inseparable mixture
3	i) Et_3N, TMSOTf ii) LiHMDS	i) CH_2Cl_2 ii) DMF	i) 0°C to rt ii) rt	i) full conversion ii) desilylated side-product
4	KOH, TBAB	toluene/H_2O	rt to 40°C	no conversion
5	TBAOH	MeOH/*i*-PrOH	rt to 50°C	complex mixture
6	pyrrolidine	MeOH	0°C to rt	complex mixture

[a] monitored by ^{1}H NMR spectroscopy.

In order to prevent α-allyloxy ketones from undergoing the competing [3,3]-Claisen rearrangement, the groups of M. Koreeda and D. Enders investigated carbanions derived from α-allyloxy hydrazones as protected substrates in the [2,3]-Wittig rearrangement process.[175] To test if the hydrazone derivative of substrate **2.79** would undergo a [2,3]-sigmatropic rearrangement, we synthesized α-crotyloxy *N,N*-dimethylhydrazone **2.87**: α-hydroxy ketone **2.86** was treated with 1,1-dimethylhydrazine to form the α-hydroxy hydrazone, which was *O*-crotylated using sodium hydride and crotyl bromide. Unfortunately, when **2.87** was subjected to the described reaction conditions (KH, *t*-BuOH/THF, 0°C or *t*-BuLi, THF, –100°C to 0°C), we did not observe formation of any [2,3]-rearranged product (Scheme 2.38).



2.86, *dr* 3:2 **2.87**, 36 % over 2 steps

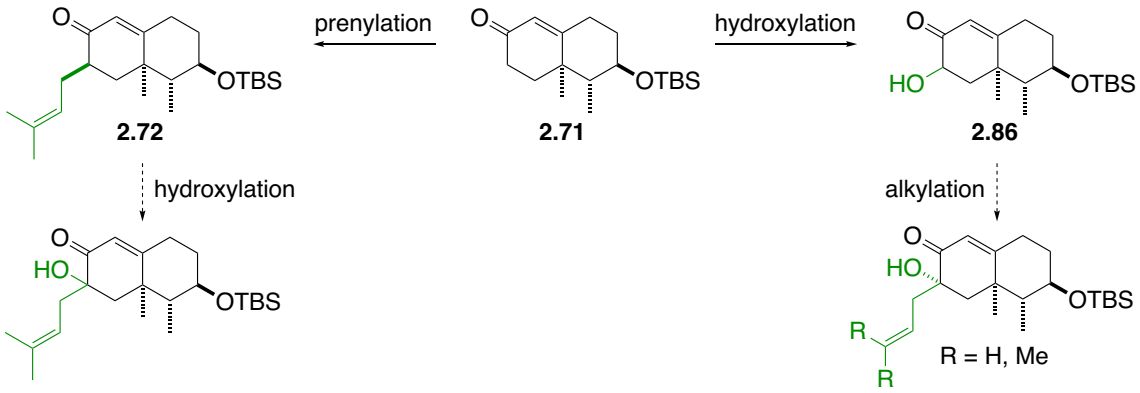
[174] A. McNally, B. Evans, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2006**, *45*, 2116-2119.

[175] J. I. Luengo, M. Koreeda, *J. Org. Chem.* **1989**, *54*, 5415-5417; D. Enders, M. Bartsch, D. Backhaus, J. Runsink, G. Raabe, *Synthesis* **1996**, 1438-1442.

Scheme 2.38: Synthesis of α-crotyloxy *N,N*-dimethylhydrazone **2.87** and attempted [2,3]-Wittig rearrangement. Reaction conditions: a) KH, *t*-BuOH/THF, 0°C, complex mixture; b) *t*-BuLi, THF, –100°C to 0°C, complex mixture.

2.2.5 Approach Featuring C7 Hydroxylation on the Bicyclic System

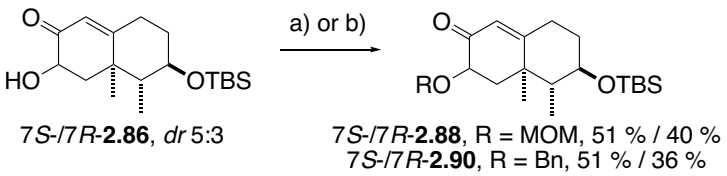
In the following approach, we elaborated an alternative route for the installation of the C7 carbinol. A multi-step sequence comparable to the late-stage C7 hydroxylation approach (section 2.2.3) was designed. Starting from octalone **2.71**, two possible pathways can be considered as summarized in Scheme 2.39: either α-hydroxylation of prenylated octalone **2.72** in order to install the C7 carbinol as a second step, or introduction of an allyl or prenyl group by α-alkylation at position C7 in octalone **2.86** formed by hydroxylation of C7. Hydroxylation of the prenylated octalone **2.72** was considered problematic due to stereoselectivity issues, keeping in mind that hydroxylation of octalone **2.71** had resulted in a diastereomeric mixture of 3:2, as described in the previous section (2.2.4). In contrast, prenylation of octalone **2.71** furnished the desired isomer with a diastereomeric ratio of >10:1. Therefore, we decided to start our investigations on the latter approach.



Scheme 2.39: Stereoselective elaboration of the C7 carbinol by hydroxylation and alkylation.

2.2.5.1 Installation of the C7 Carbinol by Early-Stage Hydroxylation

Before we started to investigate the C7 alkylation of the α-hydroxy ketone **2.86**, we first had to identify an appropriate protecting group for the secondary alcohol under the premise that the reaction conditions for its cleavage should be orthogonal to those needed for removal of the TBS protecting group. Additionally, the protecting group for the secondary alcohol should not be too sterically demanding, since a bulky group at this position would perturb the alkylation process. We first opted for the methoxymethyl (MOM) group, and MOM ether **2.88** was synthesized in 91 % yield by treating α-hydroxy ketone **2.86** with MOMBr and DIPEA in CH_2Cl_2 at 40°C (Scheme 2.40).



7*S*-/7*R*-**2.86**, *dr* 5:3

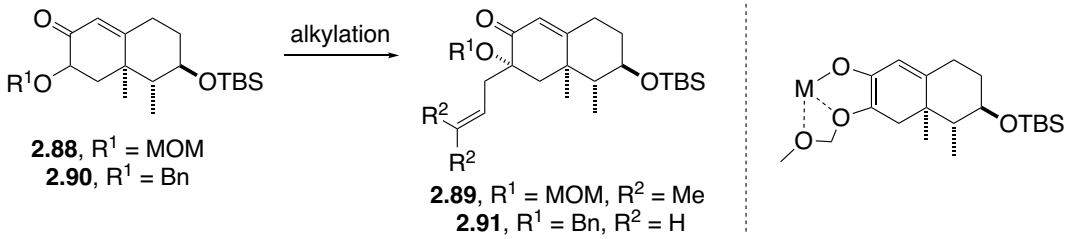
7*S*-/7*R*-**2.88**, R = MOM, 51 % / 40 %
7*S*-/7*R*-**2.90**, R = Bn, 51 % / 36 %

Scheme 2.40: Protection of α-hydroxy ketone **2.86**. Reaction conditions: a) MOMBr, DIPEA, CH_2Cl_2, 40°C; b) BnBr, Ag_2O, CH_2Cl_2, rt.

Selected screening conditions for the alkylation of MOM-protected α-hydroxy ketone **2.88** are summarized in Table 2.4 (entries 1–4). No prenylated product was formed using LiHMDS or LDA in the presence of DMPU in THF at –78°C, followed by addition of prenyl bromide and TBAI and warming to room temperature (entries 1 and 2). Using a large excess of NaH, prenyl bromide and TBAI in DMF (entry 4) resulted in formation of traces of the desired alkylated product **2.89**. However, we were not able to reproduce this result or improve the conversion by adjusting the reaction conditions. Using less equivalents of reagents resulted in no conversion, and higher reaction temperatures (0°C or room temperature) led to decomposition of the starting material. Therefore, we investigated the accessibility of the proton at C7 of **2.88** towards deprotonation. Different bases (LDA, LiHMDS, NaHMDS, KHMDS) were tested at different temperatures (–78°C to –20°C). After treating the compounds in THF at –78°C with the appropriate base, quenching with MeOD-d_4 or D_2O was performed. The experiments revealed that the cleanest conversion took place at –78°C, though with a maximum conversion of only 50 %. At higher temperatures (–40°C or –20°C), significant side product formation was observed. We assume that the enolate derived from MOM-protected α-hydroxy ketone **2.88** upon deprotonation at C7 might be stabilized by interaction of the alkali metal cation with the additional oxygen atom of the protecting group, *i.e.* formation of a seven-membered chelate ring (scheme in Table 2.4). Thus, this intermediate might not be reactive enough for alkylation. Therefore, we investigated the alkylation of a benzyl-protected substrate: benzyl ether **2.90** was synthesized in a yield of 91 % by treating a diastereomeric mixture of α-hydroxy ketone **2.86** with BnBr and Ag_2O in CH_2Cl_2 at room temperature overnight. Initial alkylation attempts showed around 20 % conversion using the reagent allyl iodide (Table 2.4, entry 6). Increasing the concentration of reagents (entry 7) as well as addition of LiCl (entry 8) did not influence the reaction outcome. Experiments for the benzyl-protected substrate were run at –78°C and slowly warmed up to 15°C or room temperature overnight. By gradually warming up the reaction mixture, we found that careful control of the reaction temperature was key for this transformation: at temperatures lower than –40°C, no reaction took place; temperatures above –35°C led to formation of significant amounts of side products (entries 9–

10). Best results were obtained when stirring a mixture of **2.90** with 2.4 equivalents of LiHMDS for one hour at –78°C, before four equivalents of DMPU were added. After stirring had been continued for 30 minutes, eight equivalents of allyl iodide (freshly filtered over K_2CO_3) were added and the mixture was stirred at a temperature between –39.5 and –35.5°C for six hours. Strictly following this optimized protocol, the desired product **2.91** was isolated in 75 % yield (entry 11).

Table 2.4: Selected screening conditions for the alkylation of protected secondary alcohol **2.88** and **2.90**.



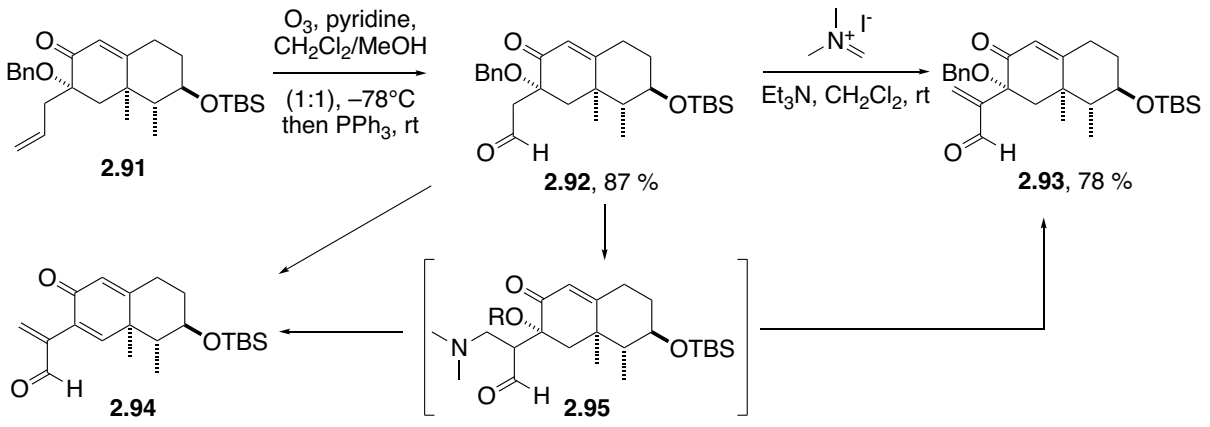
2.88, R^1 = MOM
2.90, R^1 = Bn

2.89, R^1 = MOM, R^2 = Me
2.91, R^1 = Bn, R^2 = H

entry	R^1	conditions	observations
1	**MOM**	LiHMDS (1.5 equiv.), DMPU (4 equiv.), THF, –78°C then prenyl bromide (4 equiv.), TBAI (4 equiv.), –78°C to rt	epimerization at C7, no alkylated product[a]
2	**MOM**	LDA, DMPU, THF, –78°C then prenyl bromide, TBAI, –78°C to rt	no conversion[a,b]
3	**MOM**	NaH (3 equiv.), DMF, –40°C then prenyl bromide (4 equiv.), TBAI (4 equiv.), –40°C to rt	no alkylated product[a,b]
4	**MOM**	NaH (100 equiv.), DMF, –40°C then prenyl bromide (50 equiv.), TBAI (10 equiv.), –40°C to rt	low conversion to alkylated product[a] not reproducible
5	**Bn**	LiHMDS (2 equiv.), DMPU (12 equiv.), THF, –78°C then prenyl bromide (4 equiv.), NaI (4 equiv.), –78°C to rt, o.n.	20 % conversion[a]
6	**Bn**	LiHMDS (2 equiv.), DMPU (4 equiv.), THF, –78°C then allyl iodide (4 equiv.), –78°C to 15°C, o.n.	20 % conversion[a]
7	**Bn**	LiHMDS (4 equiv.), DMPU (10 equiv.), THF, –78°C then allyl iodide (10 equiv.), –78°C to 15°C, o.n.	20 % conversion[a]
8	**Bn**	LiHMDS (2 equiv.), DMPU (4 equiv.), LiCl (4 equiv.), THF, –78°C then allyl iodide (8 equiv.), –78°C to rt, o.n.	low conversion[b]
9	**Bn**	LiHMDS (2 equiv.), DMPU (4 equiv.), LiCl (4 equiv.), THF, –78°C then allyl iodide (4 equiv.), –40°C - –35°C, 3 h	2:3 (**2.91**/**2.90**)[a] 22 %[c] (52 % brsm)
10	**Bn**	LiHMDS (2 equiv.), DMPU (4 equiv.), LiCl (4 equiv.), THF, –78°C then allyl iodide (8 equiv.), –40°C - –35°C, 3 h	1:1 ratio of **2.91**/**2.90**[a]
11	**Bn**	LiHMDS (2.4 equiv.), THF, –78°C, 1 h then DMPU (4 equiv.), –78°C, 30 min then allyl iodide (8 equiv.), –39.5°C - –35.5°C, 6 h	75 %[c]

[a] monitored by ^{1}H NMR spectroscopy; [b] monitored by thin layer chromatography of aliquot samples drawn from the reaction mixture; [c] isolated yield after column chromatography.

The terminal double bond of the benzyl-protected carbinol **2.91** was cleaved by ozonolysis to give the aldehyde **2.92** in 87 % yield, before the methylene group was installed by Eschenmoser methenylation (Scheme 2.41). Although a small-scale approach delivered 78 % of the desired product **2.93** using Eschenmoser's salt and Et_3N in CH_2Cl_2, this reaction was not reproducible on larger scale and elimination of the tertiary OBn group was observed to form dienone **2.94** as main product. Using freshly recrystallized Eschenmoser's salt (sulfolane, 140°C) did not alter the reaction outcome. Under the given reaction conditions (5 equiv. Eschenmoser's salt, 10 equiv. base), the (dimethylamino)methyl intermediate **2.95**, formed by Mannich-type reaction of the enolized carbonyl with the iminium ion of Eschenmoser's salt, was not observed due to elimination to **2.93** or double elimination to **2.94**. With lower concentrations of base (4 equiv.) and reagent (2 equiv.) formation of a 1:1 mixture of methenylated product and intermediate **2.95** was observed by ^{1}H NMR spectroscopy. When the crude product of a reaction on the 20 mg scale was dissolved in CH_2Cl_2 and stirred in the presence of SiO_2 for 90 minutes at room temperature, a mixture of the desired product **2.93** and dienone **2.94** in a 2:1 ratio was formed. Unfortunately, we were not able to reproduce this reaction outcome on a 100 mg scale and only isolated 18 % of the target compound **2.93**. Best results for a small-scale approach were obtained by using three equivalents of Eschenmoser's salt and six equivalents of base. However, when five 20 mg scale reactions were performed in parallel under identical conditions, a different ratio of products was observed in each of these batches. Since the reaction mainly showed problems on a larger scale, screening of reaction conditions was cumbersome, and we could not identify a set of reaction conditions reproducibly favoring the desired product, *viz.* triggering elimination only for the tertiary amine and not the OBn group.

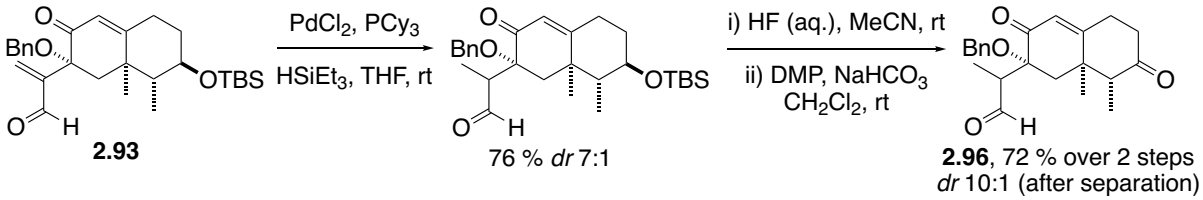


Scheme 2.41: Side chain modification of benzyl ether **2.91** by ozonolysis and methenylation.

To further optimize this reaction, one might consider using only one equivalent of base and reagent with the aim to obtain intermediate **2.95**, which could be converted to the alkene

by *N*-methylation and Hofmann elimination or by oxidation to the corresponding *N*-oxide to induce a Cope elimination, and thus avoid basic or acidic conditions triggering the side reaction. This approach was investigated by treating aldehyde **2.92** with LiHMDS (1.2 equiv.) at –78°C, before Eschenmoser's salt (2.5 equiv.) was added and the mixture was allowed to warm to room temperature. Unfortunately, formation of a complex mixture was observed. Using paraformaldehyde and freshly prepared diisopropylammonium trifluoroacetate (1.0 equiv.) in THF gave dienone **2.94** along with unidentified byproducts.[176] Stirring a mixture of aldehyde **2.92** and formaldehyde in aqueous isopropanol in the presence of a catalytic amount of pyrrolidine and propionic acid led to formation of a 5:2 mixture of dienone **2.94** and desired product **2.93**, along with other side products.[177] α-Methylation of the aldehyde **2.92** by formation of the enolate (LiHMDS, THF, –78°C) and subsequent alkylation with MeI gave no conversion at lower temperatures (–78°C, –30°C) and decomposition of the starting material when warmed up to room temperature. The same results were obtained when the corresponding dimethylhydrazone derivative of aldehyde **2.92** (dimethylhydrazine, THF, 0°C to room temperature) was subjected to the identical α-methylation conditions.

Although we could not elaborate an optimized procedure for the installation of C13, we proceeded with the ensuing steps of the synthetic route, including reduction of the enal and A-ring modifications. Conditions used for the substrate **2.74** lacking the OBn group (see chapter 2.2.3) have been successfully applied for substrate **2.93** and we obtained the tricarbonyl compound **2.96** in 55 % yield over three steps (Scheme 2.42).



Scheme 2.42: Side chain and A-ring modifications for benzyl ether substrate **2.93**.

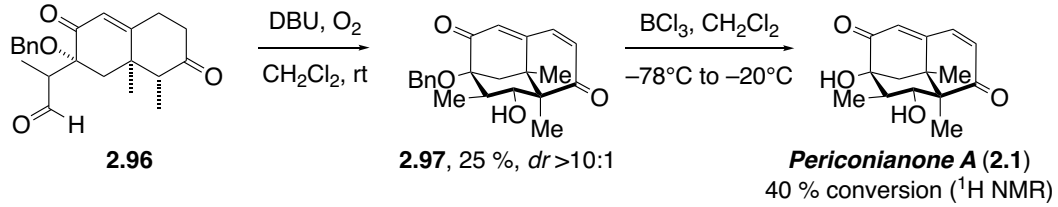
2.2.5.2 Endgame: Aldol Cyclization, Dehydrogenation and Deprotection

With tricarbonyl compound **2.96** in hand, we tested the same conditions for the aldol cyclization step as in the late-stage C7 hydroxylation approach (see chapter 2.2.3) by treating **2.96** with DBU at room temperature for three hours. Unfortunately, the starting material decomposed and no desired aldol product was detected after work-up and analysis of the crude

[176] A. Bugarin, K. D. Jones, B. T. Connell, *Chem. Commun.* **2010**, *46*, 1715-1717.

[177] A. Erkkilä, P. M. Pihko, *J. Org. Chem.* **2006**, *71*, 2538-2541.

product's ^{1}H NMR spectrum. Therefore, we performed the reaction at 0°C and isolated a new compound after the mixture had been stirred for three hours, worked up and separated by preparative TLC. However, this new compound was not identified as the expected aldol product and additional to the proton at C7, other olefinic protons were visible in the ^{1}H NMR spectrum. After structure elucidation based on 2D NMR, the new compound was identified as the diene dione **2.97**. Under the given reaction conditions, autoxidation of the C1–C2 bond took place to form the desired conjugated diene dione moiety. Subsequent experiments (see section 2.2.6.2) showed that this oxidation process only takes place on the bicyclic system and was not observed for the isolated tricyclic aldol product **2.98** when treated with DBU. As the observed autoxidation is an irreversible process, this might be explained by a late transition state for this transformation together with better stabilization by p-orbital overlap of the adjacent double bonds in the diene system of the bicyclic oxidation product, compared to the diene in the tricyclic system **2.97**, due to higher geometric strain in the latter. Since the crude mixture mainly comprised unidentified decomposition products and only traces of the tricycle **2.97**, we performed the reaction at –4°C. Conversion of the starting material to both product and side products was significantly slower and the reaction had to be stirred for two days until aldehyde **2.96** was fully consumed. Purification of the crude mixture gave tricycle **2.97** in 20 % yield and a diastereomeric ratio of >10:1. When the initial experiment at room temperature was repeated with three equivalents of DBU under an oxygen atmosphere, **2.97** was isolated in 25 % yield. Experiments using K_2CO_3 in a MeOH/THF mixture at 0°C or room temperature formed only complex mixtures.



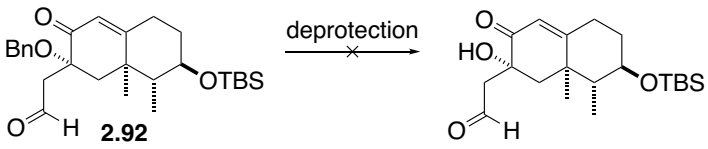
Scheme 2.43: Endgame by aldol cyclization and deprotection of the benzyl group.

The last step of this synthetic route consisted in deprotection of the tertiary alcohol at C7. Being aware of the sensitive diene dione moiety and the secondary alcohol at C12, we tested conditions that showed most promising results on the AB-ring system **2.91**, which will be discussed in the following section 2.2.5.3. However, stirring a mixture of **2.97** and BCl_3 in CH_2Cl_2 at –50°C did not initiate debenzylation and the mixture was gradually warmed in steps of 10°C, until monitoring by TLC showed conversion at –20°C. After quenching and usual work-up procedure, 40 % conversion to periconianone A (**2.1**) was indicated by ^{1}H NMR

spectroscopy (Scheme 2.43). No conversion was monitored when adding the cation scavenger pentamethylbenzene to the reaction mixture.[178]

2.2.5.3 Optimization of the Methenylation Reaction

Due to the elimination of the OBn group encountered during the methenylation of aldehyde **2.92**, we tested if the unprotected carbinol at C7 might be a more suitable substrate in this reaction. Several protocols for removal of the benzyl group were unsuccessful using aldehyde **2.92** as substrate. Although hydrogenolysis (H_2, Pd/C, EtOAc, rt) removed the benzyl group, decomposition of the aldehyde was observed. Catalytic transfer hydrogenation (ammonium formate, Pd/C, MeOH, reflux)[179] showed low conversion to different side products. Although benzyl ethers are usually not sensitive to cleavage by DDQ, a few protocols for deprotection of tertiary benzyl ethers using this reagent have been described.[180] Unfortunately, only a complex mixture was formed using DDQ in a 20:1 mixture of CH_2Cl_2 and water. The radical anion of di-*tert*-butylbiphenyl (prepared by adding Li to a solution of di-*tert*-butylbiphenyl at 0°C)[181] in THF at –78°C gave a mixture of different compounds and traces of the known aldehyde **2.73** lacking the C7 hydroxy group. This indicates that reductive cleavage of the C7–O bond instead of the $ArCH_2$–O bond took place.



Scheme 2.44: Benzyl deprotection attempts on aldehyde **2.92**.

Applying the Lewis acid BCl_3 at different temperatures (–78°C, –60°C, –40°C, –20°C, 0°C, rt) was unsuccessful, too. However, applying the latter conditions (BCl_3, CH_2Cl_2, –78°C to rt) for allylated compound **2.91** led to significant formation of **2.99**. Besides deprotection of the benzyl group, partial removal of the TBS group was observed. Key for the optimization of reaction conditions was adding the reagent at –78°C, before the mixture was warmed up to

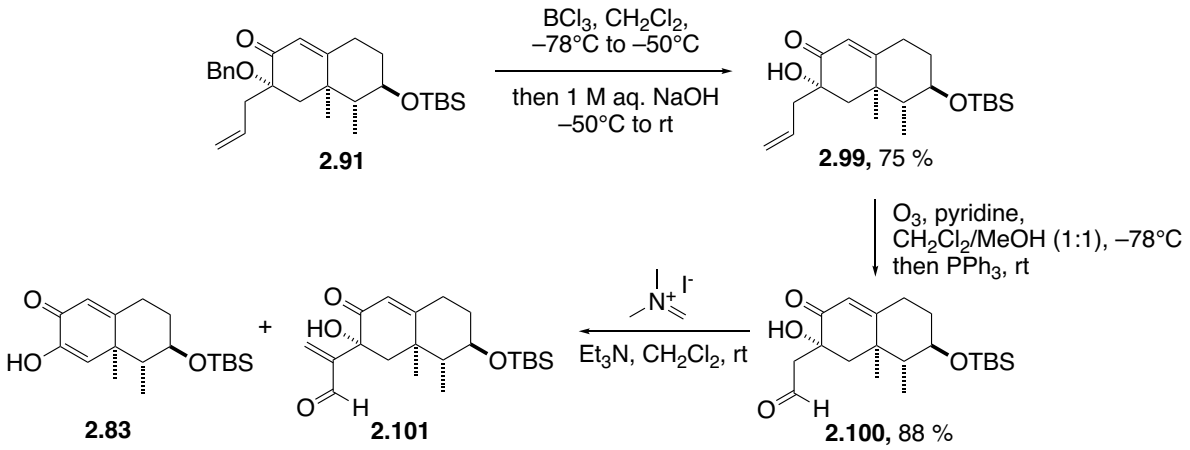
[178] X.-D. Ren, N. Zhao, S. Xu, H.-N. Lü, S.-G. Ma, Y.-B. Liu, Y. Li, J. Qu, S.-S. Yu, *Tetrahedron* **2015**, *71*, 4821-4829; K. Okano, K. I. Okuyama, T. Fukuyama, H. Tokuyama, *Synlett* **2008**, 1977-1980.

[179] T. Bieg, W. Szeja, *Synthesis* **1985**, 76-77.

[180] E. Vedejs, R. A. Buchanan, Y. Watanabe, *J. Am. Chem. Soc.* **1989**, *111*, 8430-8438; A. F. Sviridov, M. S. Ermolenko, D. V. Yashunsky, V. S. Borodkin, N. K. Kochetkov, *Tetrahedron Lett.* **1987**, *28*, 3839-3842; T. Tanaka, Y. Oikawa, N. Nakajima, T. Hamada, O. Yonemitsu, *Chem. Pharm. Bull.* **1987**, *35*, 2203-2208; N. Ikemoto, S. L. Schreiber, *J. Am. Chem. Soc.* **1992**, *114*, 2524-2536; Y. Oikawa, K. Horita, O. Yonemitsu, *Tetrahedron Lett.* **1985**, *26*, 1541-1544.

[181] P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1980**, *45*, 1924-1930; S. J. Shimshock, R. E. Waltermire, P. DeShong, *J. Am. Chem. Soc.* **1991**, *113*, 8791-8796.

–50°C and stirred at this temperature for one hour. Typical protocols recommend to quench the reaction mixture with MeOH.[178] However, carefully quenching the solution at –50°C by aqueous 1 M NaOH solution before warming up to room temperature significantly improved the outcome of the reaction with 75 % yield for carbinol **2.99**. For larger scale experiments, addition of the cation scavenger pentamethylbenzene was found to improve the yield.[178b]



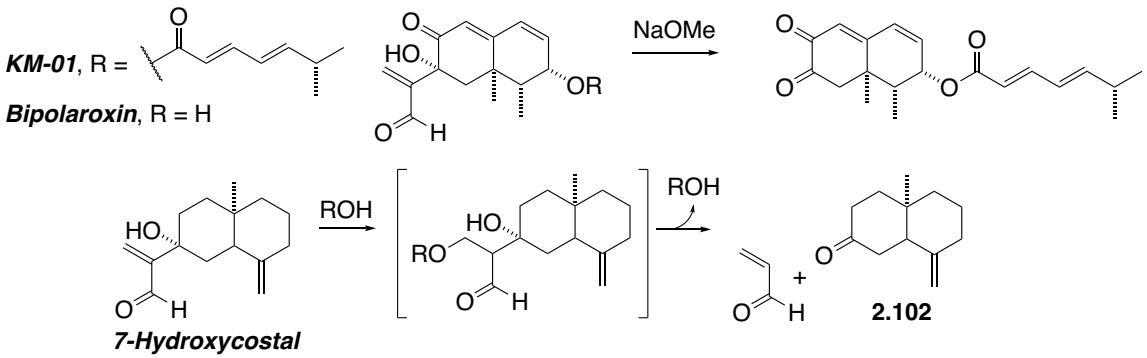
Scheme 2.45: Benzyl deprotection of allylated substrate **2.91** and side chain modification by ozonolysis and methenylation reaction in the presence of the unprotected tertiary carbinol at C7.

Ozonolysis of the deprotected substrate **2.99** gave β-hydroxy aldehyde **2.100** in 88 % yield. However, ratios between 3:1 and 3:2 for diosphenol **2.83** and enal **2.101** (Scheme 2.45) were observed after subjecting the aldehyde to methenylation conditions (3.0 equiv. of Eschenmoser's salt, 6.0 equiv. of Et_3N). Changing the base to LiHMDS (1.5 equiv.) at –78°C showed clean conversion to diosphenol **2.83**. Similar results of an eremophilane forming its corresponding trinor-eremophilane under basic conditions (NaOMe) have been reported for the brassinolide-inhibitor KM-01 by S. Kim *et al.* (Scheme 2.46).[182] Studies on the phytoalexin 7-hydroxycostal, an eudesmane-type sesquiterpene, revealed the hydroxy-enal moiety to be implicated in its antifungal activity.[183] Incubation experiments in sweet potato culture medium showed degradation of 7-hydroxycostal to ketone **2.102**. Therefore, a mechanistic pathway of conjugate addition of a nucleophile to the enal followed by a fragmentation to release acrolein, formally a retro-Baylis-Hillman-type reaction, was proposed. Based on this report and the known phytotoxicity of acrolein, the group of J. Clardy suggested a similar mechanism for the

[182] S.-k. Kim, M. Hatori, M. Ojika, Y. Sakagami, S. Marumo, *Bioorg. Med. Chem.* **1998**, *6*, 1975-1982.

[183] J. A. Schneider, K. Nakanishi, *J. Chem. Soc., Chem. Commun.* **1983**, 353-355.

host-selective phytotoxin bipolaroxin.[184] Experiments to chemically prove this proposed biosynthetic transformation have already been attempted on monocyclic test-substrates without success.[185] Therefore, it would not only be interesting to investigate the observed reaction for bipolaroxin, but also to clarify whether diosphenol **2.83** is formed by retro-aldol reaction of aldehyde **2.100** in the presence of base, or whether it first reacts to the (dimethylamino)methyl intermediate, which can undergo the retro-Baylis-Hillman process.

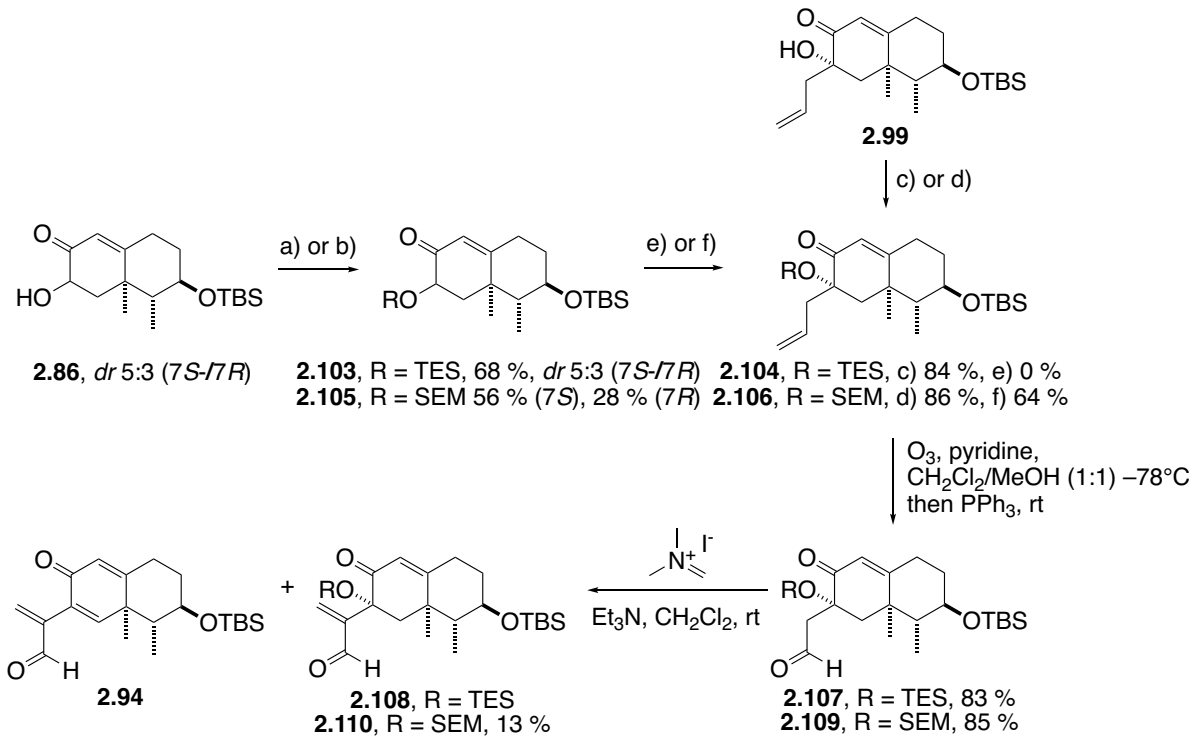


Scheme 2.46: Formation of trinor-eremophilanes by a proposed retro-Baylis-Hillman-type reaction.

To avoid formation of dienone **2.94**, observed during the methenylation procedure of benzyl-protected aldehyde **2.92**, as well as diosphenol **2.83**, observed for free carbinol **2.100**, we envisioned to test different silyl protecting groups at C7–OH in this transformation. Protection of the secondary alcohol with TESCl and imidazole in CH_2Cl_2 formed the desired silyl ether **2.103** in 68 % yield. Unfortunately, alkylation attempts to form the tertiary silyl-protected carbinol **2.104** were not successful and no conversion was observed, not even at room temperature. Nevertheless, we were able to protect tertiary carbinol **2.99** by using TESOTf and 2,6-lutidine in CH_2Cl_2 at 0°C in 84 % yield, after the milder conditions used previously for protection of the secondary alcohol **2.103** (TESCl, imidazole, CH_2Cl_2, rt) showed no conversion. SEM-protected carbinol was synthesized using both pathways: protection using SEMCl and DIPEA in CH_2Cl_2 at room temperature gave the protected isomers 7*S*- and 7*R*-**2.105** in a combined yield of 84 %. Modifying the alkylation conditions optimized for the benzylated compound **2.90** by applying higher temperatures (–36°C to –32°C) gave the desired SEM carbinol **2.106** in 64 % yield. Alternatively, **2.106** was synthesized by protection of free carbinol **2.99** using SEMCl and DIPEA in CH_2Cl_2 at room temperature.

[184] F. Sugawara, G. Strobel, L. E. Fisher, G. D. Van Duyne, J. Clardy, *Proc. Natl. Acad. Sci. U. S. A.* **1985**, *82*, 8291-8294.

[185] Z. Lidert, S. F. Williams, A. B. Holmes, *Tetrahedron Lett.* **1988**, *29*, 1347-1350.



Scheme 2.47: TES and SEM protection, ozonolysis and methenylation attempts for the protected substrates **2.104** and **2.106**. Reaction conditions: a) TESCl, imidazole, CH_2Cl_2, rt; b) SEMCl, DIPEA, CH_2Cl_2, rt; c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C; d) SEMCl, DIPEA, CH_2Cl_2, rt; e) LiHMDS, THF, –78°C, 1 h, then DMPU, –78°C, 30 min, then allyl iodide, –38°C, 3 h, –20°C, 15 h, 0°C, 3 h, rt, 3 h; f) LiHMDS, THF, –78°C, 1 h, then DMPU, –78°C, 30 min, then allyl iodide, –36°C - –32°C, 21 h.

Cleavage of the terminal double bond in **2.104** and **2.106** by ozonolysis (O_3, pyridine, CH_2Cl_2/MeOH, –78°C; then PPh_3, rt) was performed in high yield and set the stage for the methenylation. Methenylation (5 equiv. Eschenmoser's salt, 10 equiv. Et_3N, CH_2Cl_2, rt, 3 h) of TES-protected carbinol **2.107** gave a 7:1 mixture of the corresponding (dimethylamino)methyl intermediate (*dr* 4:3 at C11) and starting material. Stirring this mixture and SiO_2 in CH_2Cl_2 for 2.5 hours resulted in a 4:3:1 mixture of dienone **2.94**, desired enal **2.108** and starting material, respectively. Using a lower amount of the reagents (3 equiv. Eschenmoser's salt, 6 equiv. Et_3N) only gave 30 % conversion to the (dimethylamino)methyl intermediate. Eschenmoser methenylation of SEM-protected carbinol **2.109** did not give the (dimethylamino)methyl intermediate, but a mixture of desired product **2.110** and dienone **2.94**. Similar to the reactions with the benzyl and TES-protected carbinols, these experiments were not reproducible. Although screening different bases (Et_3N, DIPEA, DBU) and concentrations of both reagents (base and Eschenmoser's salt), optimization of the reaction conditions to trigger product formation failed. Most promising results with a 5:2 ratio of desired product **2.110** and dienone **2.94** were obtained using three equivalents of Eschenmoser's salt and six equivalents of DIPEA

in CH_2Cl_2 at room temperature with stirring for three hours. Applying these reaction conditions on a larger scale gave a 1:2 ratio of **2.110** and **2.94** (crude product ^{1}H NMR spectrum) and an isolated yield of only 13 % for the desired product **2.110** after column chromatography.

2.2.6 Successful Approach to Periconianone A by a Formal [2,3]-Wittig Rearrangement

2.2.6.1 Installation of the C7 Carbinol

Based on the findings that in the presence of $Rh_2(OAc)_4$, diazoketone **2.82** reacted with *trans*-crotyl alcohol in a tandem O–H insertion/Claisen-rearrangement to furnish α-allylated α-hydroxyketone **2.84** (see chapter 2.2.4), we investigated the feasibility of a [1,2]-shift of the four carbon fragment from C8 to C7 in **2.84**, aiming to obtain the formal [2,3]-rearranged product **2.80** (Scheme 2.48). [1,2]-Alkyl or -aryl migrations in α-hydroxy ketones or aldehydes are termed α-ketol or acyloin rearrangement. The synthetic value of this transformation has been considerably increased since its discovery in the D-ring homoannulation of steroids.[186] Nevertheless, it is rarely used in total synthesis[187] and most of the reported reactions involving this type of rearrangement are unanticipated.[188] Mediated by Brønsted bases or acids, Lewis acids or heat, the α-ketol rearrangement is known to be a reversible process with the equilibrium usually lying on the side of the thermodynamically more stable α-hydroxy carbonyl isomer. Typical substrates that undergo this [1,2]-shift are β-hydroxy α-diketones forming the more stable β-dicarbonyl compound[189] or compounds where ring strain is released by this transformation.[186] By comparing **2.80** and **2.84**, we hypothesize that formation of a conjugated enone moiety might be the thermodynamic driving force to trigger the desired formation of **2.80**. An α-ketol rearrangement with formation of a conjugated system as thermodynamic driving force has not been reported in literature to date.

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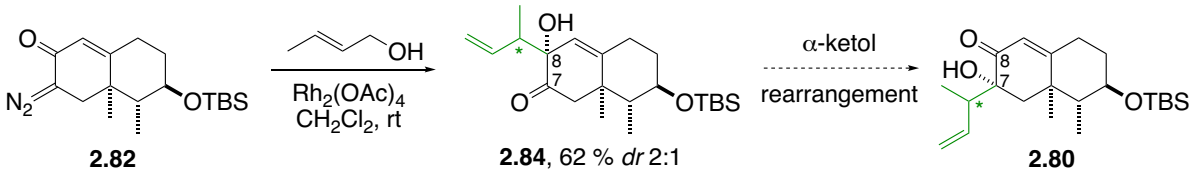
[186] N. L. Wendler, D. Taub, R. Firestone, *Experientia* **1959**, *15*, 237-239; L. A. Paquette, J. E. Hofferberth, in Organic Reactions, *Vol. 62* (Ed.: L. E. Overman), John Wiley & Sons, Inc., **2004**, pp. 477-567.

[187] Z.-L. Song, C.-A. Fan, Y.-Q. Tu, *Chem. Rev.* **2011**, *111*, 7523-7556.

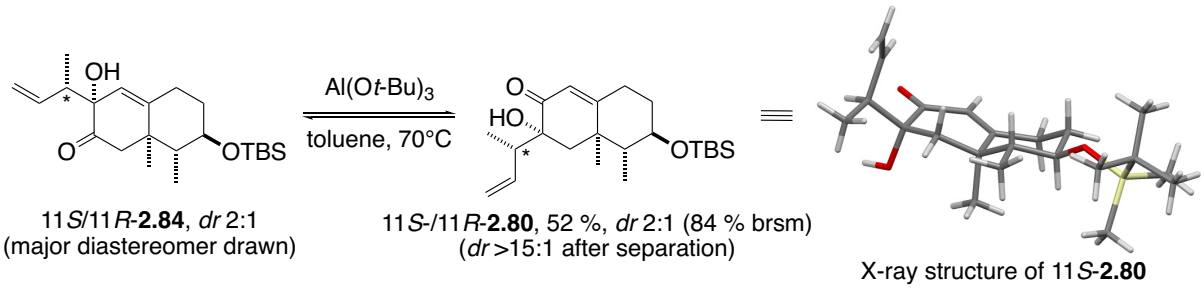
[188] T. E. Adams, M. El Sous, B. C. Hawkins, S. Hirner, G. Holloway, M. L. Khoo, D. J. Owen, G. P. Savage, P. J. Scammells, M. A. Rizzacasa, *J. Am. Chem. Soc.* **2009**, *131*, 1607-1616; S. Dong, J. Zhu, J. A. Porco, *J. Am. Chem. Soc.* **2008**, *130*, 2738-2739; B. Gerard, G. Jones, J. A. Porco, *J. Am. Chem. Soc.* **2004**, *126*, 13620-13621; K. C. Nicolaou, P. K. Sasmal, H. Xu, *J. Am. Chem. Soc.* **2004**, *126*, 5493-5501; S. Hanessian, R. Roy, *Can. J. Chem.* **1985**, *63*, 163-172; J. L. Wood, A. A. Holubec, B. M. Stoltz, M. M. Weiss, J. A. Dixon, B. D. Doan, M. F. Shamji, J. M. Chen, T. P. Heffron, *J. Am. Chem. Soc.* **1999**, *121*, 6326-6327.

[189] J.-H. Chen, S. R. Levine, J. F. Buergler, T. C. McMahon, M. R. Medeiros, J. L. Wood, *Org. Lett.* **2012**, *14*, 4531-4533; J. L. Wood, B. M. Stoltz, H.-J. Dietrich, D. A. Pflum, D. T. Petsch, *J. Am. Chem. Soc.* **1997**, *119*, 9641-9651.



Scheme 2.48: Formal [2,3]-Wittig rearrangement by O–H insertion of *trans*-crotyl alcohol into the carbenoid derived from diazoketone **2.82** and subsequent Claisen rearrangement followed by a proposed [1,2]-shift.

After initial experiments using the Lewis acid $BF_3 \cdot OEt_2$[189,190] had only triggered elimination of the tertiary alcohol to form a conjugated dienone, we were very pleased that treatment of α-allylated α-hydroxyketone **2.84** with Al(O*t*-Bu)$_3$ or Al(O*i*-Pr)$_3$ induced the [1,2]-shift.[191] The desired α-allylated hydroxyenone **2.80** was isolated in 52 % yield and retained (C7/C8/C11) diastereomeric ratio (*dr* 2:1 for C11) after treatment of **2.84** with Al(O*t*-Bu)$_3$ for 50 minutes at 70°C. The ^{1}H NMR spectrum of the crude reaction mixture showed almost no side product formation, which was confirmed by the isolation of 32 % of the starting material, giving a yield of 84 % based on recovered starting material. The diastereoisomers were separated using column chromatography, and the structure of the main isomer of **2.80** was confirmed by single-crystal X-ray analysis. Unfortunately, an *S*-configuration at C11 showed that the undesired isomer was formed preferentially in the Claisen rearrangement, assuming the α-ketol rearrangement to be a stereospecific transformation.



Scheme 2.49: α-Ketol rearrangement induced by Al(O*t*-Bu)$_3$ to form the desired C7 carbinol **2.80** (*dr* 2:1) and single crystal X-ray structure of 11*S*-**2.80**.

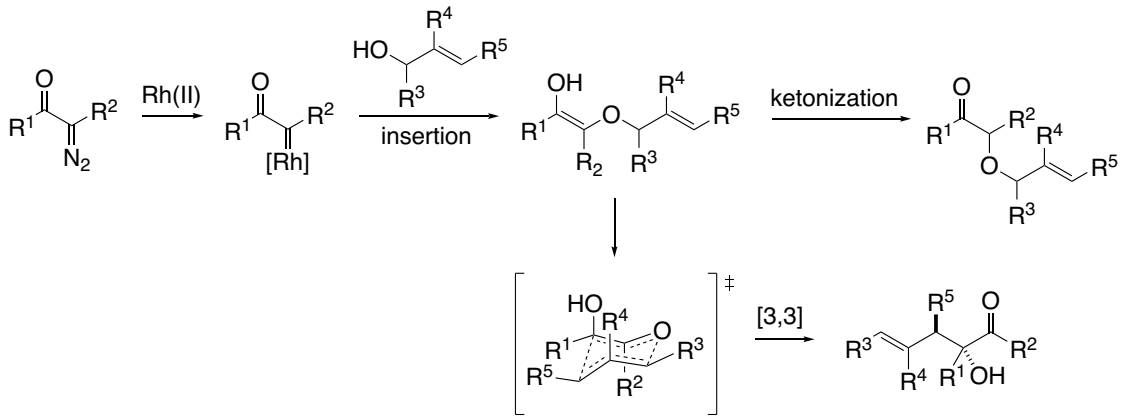
Initially, the ensuing steps of the synthesis were carried out with the obtained diastereomeric 2:1 mixture of **2.80**, since we intended to use basic conditions for the aldol addition step to construct the tricyclic skeleton, allowing for isomerization of the stereogenic center at C11 after cleaving the terminal double bond. However, while screening conditions for

[190] I. Drutu, E. S. Krygowski, J. L. Wood, *J. Org. Chem.* **2001**, *66*, 7025-7029; J. L. Wood, G. A. Moniz, *Org. Lett.* **1999**, *1*, 371-374.

[191] L. A. Paquette, J. E. Hofferberth, *J. Org. Chem.* **2003**, *68*, 2266-2275.

this cyclization reaction, which will be discussed later in this section, we found basic conditions to be unsuitable for our substrate. As the optimized reaction conditions did not induce isomerization at C11, we investigated how to trigger selective formation of the 11*R*-isomer of **2.84** in the tandem O–H insertion/[3,3]-sigmatropic rearrangement process.

The reaction of α-diazoketones with allylic alcohols in the presence of rhodium(II) to form the corresponding α-alkylated α-hydroxyketones *via* O–H insertion and spontaneous Claisen rearrangement has been reported by J. L. Wood and co-workers.[189,190,192] Mechanistically, formation of the rhodium carbene complex derived from the corresponding diazo compound by release of N_2 is followed by O–H insertion of the allylic alcohol. J. L. Wood and co-workers suggest formation of a (*Z*)-enol intermediate upon intramolecular proton transfer after the insertion step. The (*Z*)-enol intermediate can then either undergo ketonization to the α-keto ether (formal insertion product) or a subsequent [3,3]-sigmatropic rearrangement to the α-alkylated α-hydroxyketone (Scheme 2.50).

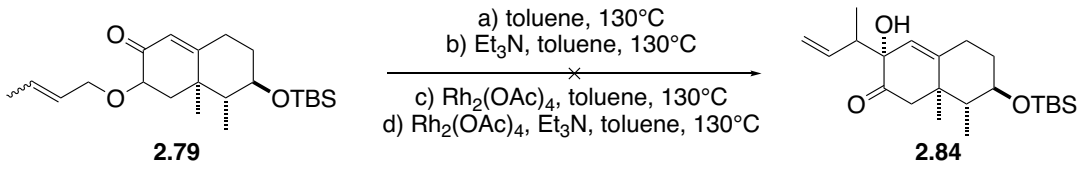


Scheme 2.50: O–H insertion of allylic alcohols into the rhodium carbene complexes derived from α-diazoketones, and [3,3]-sigmatropic rearrangement *via* a (*Z*)-enol intermediate and six-membered cyclic transition state.

Additionally, kinetic studies have been performed by J. L Wood and coworkers in order to rule out the involvement of Rh or acid in the rearrangement process.[190b] These reported observations are in accordance with our findings, as the α-keto ether byproduct **2.79** formed by keto-enol tautomerism of the central intermediate **2.111** (Scheme 2.52) did not undergo the [3,3]-sigmatropic rearrangement, even upon prolonged reaction time. Neither did isolated

[192] J. L. Wood, G. A. Moniz, D. A. Pflum, B. M. Stoltz, A. A. Holubec, H.-J. Dietrich, *J. Am. Chem. Soc.* **1999**, *121*, 1748-1749.

α-keto ether **2.79** undergo Claisen rearrangement by heating in the absence or presence of base (Et_3N) and/or in the presence of $Rh_2(OAc)_4$ under microwave irradiation (Scheme 2.51).



Scheme 2.51: Attempts to initiate the Claisen-rearrangement for isolated α-keto ether **2.79**.

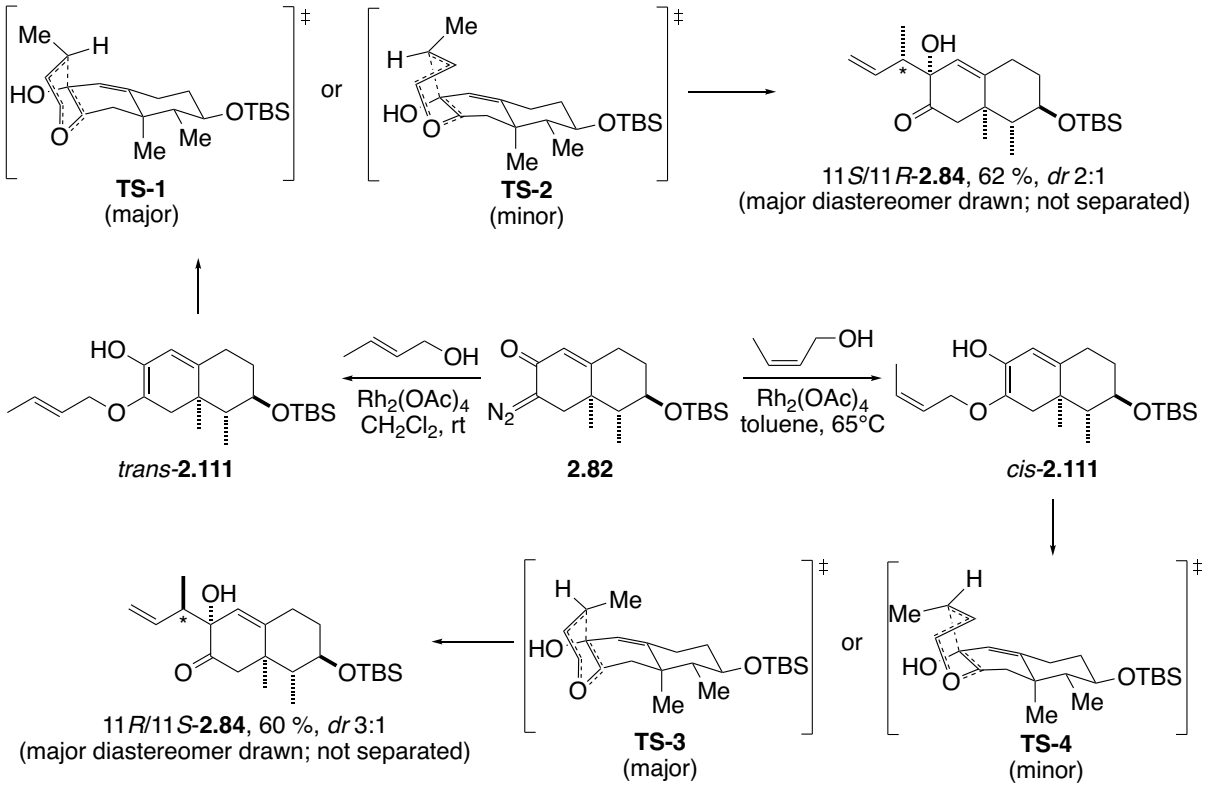
Mechanistically, we assumed that the formed enol **2.111** would undergo a concerted sigmatropic rearrangement process. Although *trans*-crotyl alcohol containing only 5 % of the *cis*-isomer was used in this reaction, we were surprised by the moderate stereochemical outcome of 2:1 (*S*/*R*) at C11 for α-alkylated α-hydroxyketone **2.84**. Stereoselectivity in the Claisen rearrangement is dictated by the geometric requirements for a cyclic transition state, and the energetic preference for chair-like transition states is well described.[193] However, for the ester enolate Claisen rearrangement the existence of both chair- and boat-like transitions states has been reported by R. E. Ireland and co-workers.[194] While acyclic substrates favor rearrangements *via* chair transition states, cyclohexenyl silyl ketene acetals can react *via* either chair or boat transitions states. Therefore, we assume that both the chair (**TS 1**) and the twist boat (**TS 2**) transition state might be accessible in this [3,3]-sigmatropic rearrangement to form both C11-diastereoisomers of α-alkylated α-hydroxyketone **2.84** (Scheme 2.52).

Aiming for the diastereoselective preparation of the 11*R*-isomer of **2.84**, we investigated the influence of choosing either *cis*- or *trans*-crotyl alcohol as starting material for the tandem O–H insertion/Claisen rearrangement process. Indeed, when *cis*-crotyl alcohol was used in this reaction sequence, we observed formation of α-alkylated α-hydroxyketone **2.84** in a diastereomeric ratio of 3:1 in favor for the 11*R*-isomer (Scheme 2.52). However, this transformation did not take place at room temperature and the reaction mixture had to be heated to 65°C. The higher activation barrier for the *cis*-substrate might be explained by the methyl group at C11 in axial position in the cyclic transition states **TS-3** and **TS-4** resulting in stronger 1,3-diaxial interactions as in **TS-1** and **TS-2** with this methyl group in equatorial position. Thus, **TS-1** and **TS-2** are proposed to be lower in energy than **TS-3** and **TS-4** (Scheme 2.52). The

[193] R. L. Vance, N. G. Rondan, K. N. Houk, F. Jensen, W. T. Borden, A. Komornicki, E. Wimmer, *J. Am. Chem. Soc.* **1988**, *110*, 2314-2315; P. Vittorelli, H.-J. Hansen, H. Schmid, *Helv. Chim. Acta* **1975**, *58*, 1293-1309; P. Vittorelli, T. Winkler, H. J. Hansen, H. Schmid, *Helv. Chim. Acta* **1968**, *51*, 1457-1461.

[194] M. M. Khaledy, M. Y. S. Kalani, K. S. Khuong, K. N. Houk, V. Aviyente, R. Neier, N. Soldermann, J. Velker, *J. Org. Chem.* **2003**, *68*, 572-577; R. E. Ireland, P. Wipf, J. N. Xiang, *J. Org. Chem.* **1991**, *56*, 3572-3582.

best conditions were found by slowly adding a solution of diazoketone **2.82** in toluene or 1,2-dichloroethane to a pre-heated (65°C) mixture of crotyl alcohol (20 equiv.) and $Rh_2(OAc)_4$ (3.5 mol%) in the same solvent, which gave the desired product in 60 % yield. Higher (100 equiv.) or lower (2 equiv.) amounts of *cis*-crotyl alcohol resulted in lower yields and formation of more side products. Instead of adding diazoketone **2.82** to a solution of $Rh_2(OAc)_4$ and crotyl alcohol, J. L. Wood and co-workers used a protocol by adding the catalyst to a solution of the reactants.[190b] By adding $Rh_2(OAc)_4$ (1 mol%) to a solution of diazoketone **2.82** and crotyl alcohol (2.5 equiv.), followed by heating to 65°C, formed 50 % of the desired compound **2.84** in a small scale approach (20 mg).



Scheme 2.52: Tandem O–H insertion and Claisen-rearrangement using either the *trans*- or *cis*-isomer of crotyl alcohol, and proposed transition states to explain the stereochemical outcome with respect to the configuration at C11.

Unfortunately, conditions used afore (Table 2.5, entry 1) for the α-ketol rearrangement of the mixture containing more of the 11*S*-isomer (2:1 11*S*/11*R*) were lower yielding when a mixture containing more of the 11*R*-isomer (3:1 11*R*/11*S*) was used as starting material (entry 2). Therefore, reaction conditions for the [1,2]-shift were screened. Since the diastereoisomers could not be separated using column chromatography after the tandem O–H insertion/Claisen rearrangement reaction, we subjected mixtures containing both 11*S*-**2.84** and 11*R*-**2.84** to several sets of reaction conditions. Increasing the concentration of Al(O*t*-Bu)$_3$ was

found to give a lower yield owing to more side product formation (entry 3). Using cyclohexane or diglyme instead of toluene as solvent did not influence the reaction outcome significantly (entries 4 and 5). An increased reaction temperature (100°C) led to more side product formation. With increased reaction time, more side products were also formed at lower temperatures (60°C or rt). Basic conditions using K_2CO_3 (entry 6), Cs_2CO_3 (entries 7 and 8)[195] or aqueous NaOH (entry 9)[196] gave low conversion. Similar results compared to the initial conditions (entry 2) were obtained using KO*t*-Bu in toluene (entry 10).[197] Unfortunately, this reaction turned out to proceed sluggishly and more side product formation was indicated by ^{1}H NMR spectroscopy of the crude reaction mixture. In a recently published report by the group of J. Zhu,[198] enantioselective α-ketol rearrangements of α-hydroxy acetals using catalytic amounts of chiral phosphoramide BINOL derivatives have been presented. In order to apply their protocol in the reaction with our substrate, we synthesized the known phosphoramide **2.112**.[199] With the reported reaction conditions, desired α-allylated hydroxyenone **2.80** was isolated in 50 % yield and 80 % based on recovered starting material (entry 11). However, while repeating the protocol for the preparation of phosphoramide **2.112**, more attention was paid to the separation by column chromatography and a minor unknown compound, initially not separated from the main product, was separated from phosphoramide **2.112**. When used as a reagent for the α-ketol rearrangement, fractions containing pure phosphoramide **2.112** showed no conversion (entry 12). However, applying the isolated phosphoramide byproduct as reagent gave 72 % yield for the desired [1,2]-rearranged product **2.80** as indicated by ^{1}H NMR spectroscopy of the crude reaction mixture (entry 13). The group of M. Rueping discovered that upon purification by column chromatography, phosphoramides can form their corresponding calcium salts due to ionic impurities in the silica gel.[200] In order to prove that the so far unknown compound triggering the desired acyloin rearrangement is the corresponding calcium salt of phosphoramide **2.112**, we stirred a mixture of purified **2.112** and $Ca(OMe)_2$ in MeOH.[201] Indeed did the ^{1}H as well as ^{31}P NMR spectra indicate the synthesized calcium salt **2.113** to be identical to the unknown compound isolated before, and it also triggered the desired ketol rearrangement.

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[195] M. Kawamura, S. Kamo, S. Azuma, K. Kubo, T. Sasamori, N. Tokitoh, K. Kuramochi, K. Tsubaki, *Org. Lett.* **2017**, *19*, 301-303.

[196] L. Leng, X. Zhou, Q. Liao, F. Wang, H. Song, D. Zhang, X.-Y. Liu, Y. Qin, *Angew. Chem. Int. Ed.* **2017**, *56*, 3703-3707.

[197] E. Mosettig, U. Beglinger, F. Dolder, H. Lichti, P. Quitt, J. A. Waters, *J. Am. Chem. Soc.* **1963**, *85*, 2305-2309.

[198] H. Wu, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5858-5861.

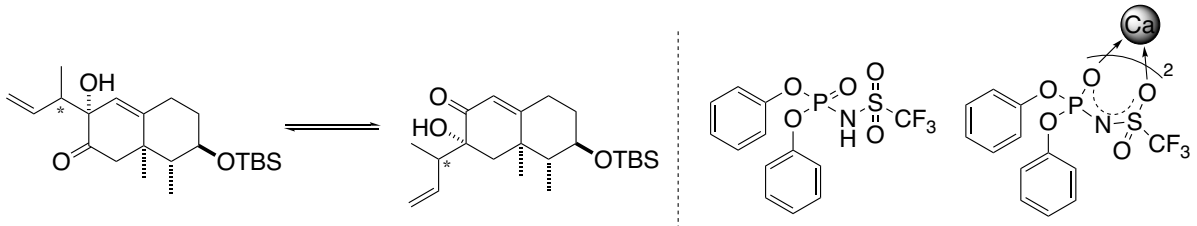
[199] K. Tomooka, M. Suzuki, M. Shimada, R. Ni, K. Uehara, *Org. Lett.* **2011**, *13*, 4926-4929.

[200] M. Rueping, B. J. Nachtsheim, R. M. Koenigs, W. Ieawsuwan, *Chem. Eur. J.* **2010**, *16*, 13116-13126.

[201] M. Rueping, T. Bootwicha, S. Kambutong, E. Sugiono, *Chem. Asian. J.* **2012**, *7*, 1195-1198.

Using a catalytic amount (10 mol%) instead of two equivalents of **2.113** slowed down the reaction and caused more side product formation, resulting in lower yields (entry 14).

Table 2.5: Selected conditions for the α-ketol rearrangement.

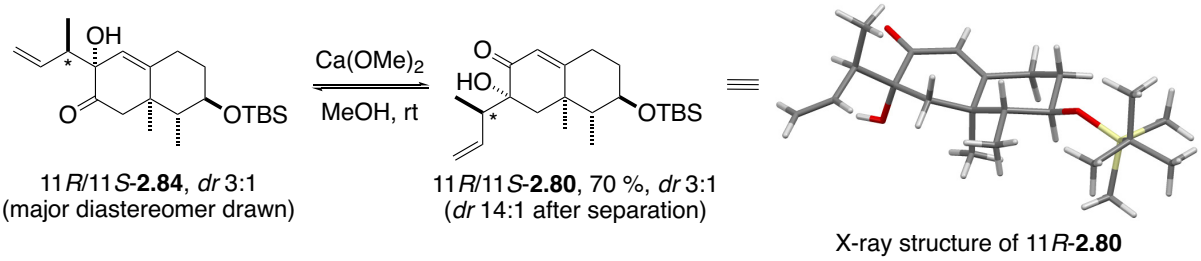


2.84 **2.80** **2.112** **2.113**

entry	reagent	solvent	temperature	time	scale	yield (^{1}H NMR)	isolated yield[c]
1[a]	Al(O*t*Bu)$_3$ (2.0 equiv.)	toluene	70°C	50 min	240 mg		52 % (84 %)
2[b]	Al(O*t*Bu)$_3$ (2.0 equiv.)	toluene	70°C	50 min	61 mg		39 % (69 %)
3[b]	Al(O*t*Bu)$_3$ (3.0 equiv.)	toluene	70°C	50 min	250 mg		33 % (56 %)
4[b]	Al(O*t*Bu)$_3$ (2.0 equiv.)	cyclohexane	70°C	50 min	3 mg	33 %	
5[b]	Al(O*t*Bu)$_3$ (2.0 equiv.)	diglyme	70°C	50 min	2 mg	35 %	
6[b]	K_2CO_3 (4.0 equiv.)	toluene	80°C	12 h	2 mg	8 %	
7[b]	Cs_2CO_3 (1.0 equiv.)	DMF	60°C	80 min	2 mg	9 %	
8[b]	Cs_2CO_3 (1.0 equiv.)	DMF	80°C	80 min	2 mg	14 %	
9[b]	NaOH (1 M)	H_2O/dioxane (1:1)	90°C	2 h	2 mg	24 %	
10[b]	KO*t*Bu (1.5 equiv.)	toluene	rt	10 min	2 mg	39 %	
11[b]	**2.112**/**2.113** (unknown ratio), 4Å MS	cyclohexane	70°C	11 h	325 mg		50 % (80 %)
12[a/b]	**2.112** (2.0 equiv.), 4Å MS	cyclohexane	70°C	9 h	2 mg	0 %	
13[a]	**2.113** (2.0 equiv.), 4Å MS	cyclohexane	70°C	9 h	2 mg	72 %	
14[a]	**2.113** (10 mol%)	cyclohexane	70°C	48 h	2 mg	58 %	
15[a]	Ca(OMe)$_2$ (2.0 equiv.)	MeOH	rt	44 h	324 mg		71 % (80 %)
16[b]	Ca(OMe)$_2$ (2.0 equiv.)	MeOH	rt	44 h	73 mg		70 %
17[a]	NaOMe (2.0 equiv.)	MeOH	rt	24 h	2 mg	0 %	

[a] 2:1 mixture of 11*S*/11*R*-**2.84** was used; [b] 3:1 mixture of 11*R*/11*S*-**2.84** was used; [c] yields based on recovered starting material are given in parentheses.

Knowing about the involvement of Ca(II) in this process, we tested if the phosphoramide could be replaced by a simpler anion. Fortunately, treatment of **2.84** with $Ca(OMe)_2$ in MeOH at room temperature induced the [1,2] shift as well, and an increased yield of 71 % (for a 2:1 mixture of 11*S*/11*R*, entry 15) or 70 % (for a 3:1 mixture of 11*R*/11*S*, entry 16) for **2.80** was obtained after purification of the reaction mixture. A test experiment replacing $Ca(OMe)_2$ with NaOMe showed no conversion (entry 17) and further substantiated Ca(II) to be essential in the presented transformation. In order to evidence the Ca(II)-mediated α-ketol rearrangement to be a reversible process, the purified products have been submitted to the same reaction conditions ($Ca(OMe)_2$, MeOH, rt, 45 hours). Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy showed a ratio of 1:5 for α-alkylated α-hydroxyketone **2.84** and α-alkylated α-hydroxyenone **2.80**. These findings further indicate the desired product **2.80** to be thermodynamically favored under the given reaction conditions. Separation of the 3:1 mixture of **2.80** (11*R*/11*S*) resulted in almost diastereopure 11*R*-α-alkylated α-hydroxyenone **2.80** (*dr* 14:1), and the structure was confirmed by single-crystal X-ray analysis (Scheme 2.53).



11*R*/11*S*-**2.84**, *dr* 3:1
(major diastereomer drawn)

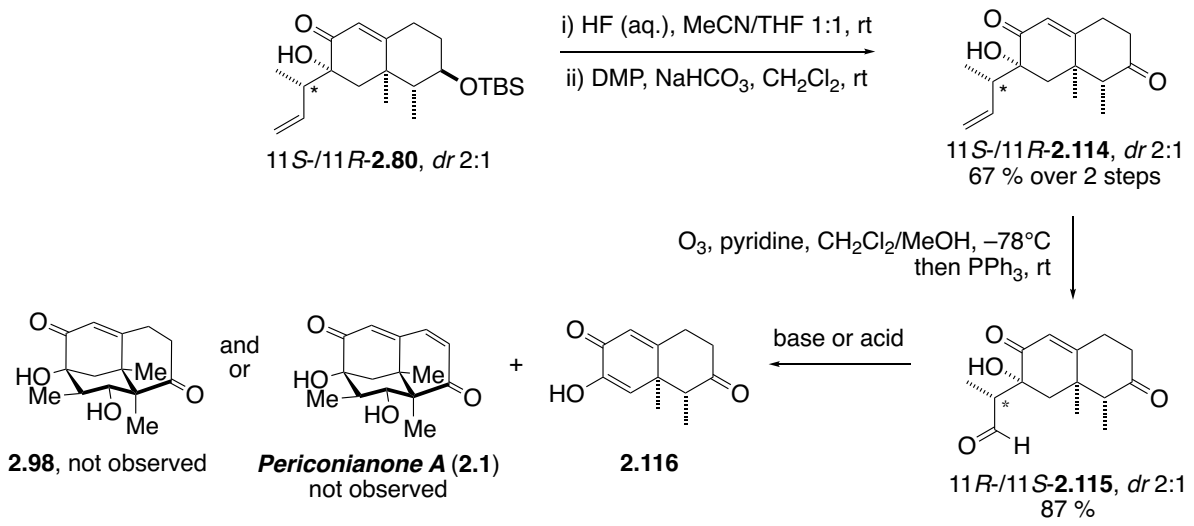
11*R*/11*S*-**2.80**, 70 %, *dr* 3:1
(*dr* 14:1 after separation)

X-ray structure of 11*R*-**2.80**

Scheme 2.53: Optimized reaction conditions for the α-ketol rearrangement of a diastereomeric 3:1 (11*R*/11*S*) mixture of **2.84** and single crystal X-ray structure of 11*R*-**2.80**.

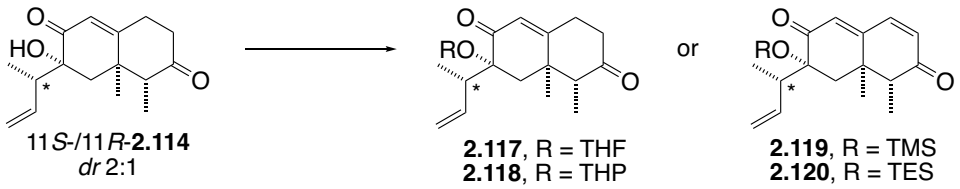
2.2.6.2 Endgame: Oxidative Modifications and Aldol Cyclization

As already mentioned (section 2.2.6.1), we anticipated that the stereogenic center at C11 would epimerize after ozonolysis of the terminal double under the basic reaction conditions used for the aldol reaction. Therefore, we initially performed the ensuing steps using a diastereomeric 2:1 (11*S*/11*R*) mixture of **2.80**. However, for analytical purposes all the reactions were also performed using diastereopure 11*S*- and 11*R*-**2.80**, respectively. Modification of the A-ring involved cleavage of the TBS group of **2.80** and oxidation of the resulting secondary hydroxy group by DMP to afford the carbonyl group at C3. Ozonolysis of the terminal double bond of **2.114** formed **2.115** and set the stage for the aldol reaction. Unfortunately, both acidic (2 M HCl, acetone, 60°C) and basic (DBU, CH_2Cl_2, 0°C or KO*t*-Bu, THF, –78°C or K_2CO_3, 18-crown-6, MeOH, rt) conditions did not give the desired tricyclic product **2.98** and led to retro-aldol reaction by cleavage of the C7–C11 bond to form diosphenol **2.116**.



Scheme 2.54: A-ring modifications and ozonolysis to form β-hydroxy aldehyde **2.115**. Retro-aldol reaction of **2.115** under basic or acidic conditions to form diosphenol **2.116**.

Table 2.6: Selected conditions for the protection of the tertiary carbinol for the dicarbonyl compound **2.114**.



entry	R	conditions	observations[a]
1	**TES**	TESOTf (2 equiv.), 2,6-lutidine (3 equiv.), CH_2Cl_2, 0°C[202]	complex mixture
2	**TMS**	TMS-imidazole, CH_2Cl_2, rt, 5 h; then reflux, o.n.[203]	no conversion
3	**TMS**	TMSI (2.5 equiv.), HMDS (4 equiv.), CH_2Cl_2, 0°C, 30 min[204]	compound **2.119** was formed, but decomposed; not reproducible
4	**THP**	DHP (4 equiv.), PPTS (10 mol%), CH_2Cl_2, rt, 2 h[205]	no conversion
5	**THP**	DHP (4 equiv.), PPTS (10 mol%), CH_2Cl_2, 45°C, 2 d additional DHP (4 equiv.) after 5 h and 8 h	compound **2.118** was formed as diastereoisomers, but in a mixture with side products
6	**THF**	DHF (20 equiv.), PPTS (10 mol%), CH_2Cl_2, rt, o.n.	complex mixture, formation of **2.117** with side products

[a] monitored by ^{1}H NMR spectroscopy.

[202] A. Nishida, I. Miyoshi, Y. Ogasawara, S. Nagumo, N. Kawahara, M. Nishida, H. Takayanagi, *Tetrahedron* **2000**, *56*, 9241-9257.

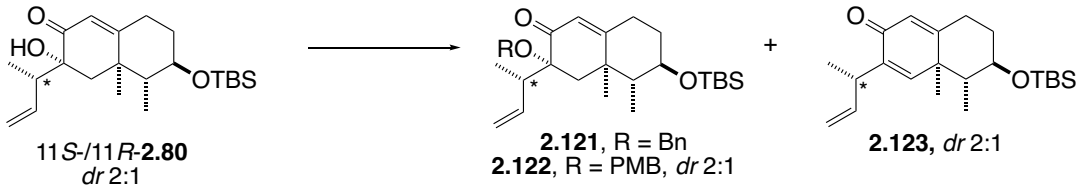
[203] L. D. Rowe, R. C. Beier, M. H. Elissalde, L. H. Stanker, R. D. Stipanovic, *Synth. Commun.* **1993**, *23*, 2191-2197.

[204] G. Y. C. Leung, H. Li, Q.-Y. Toh, A. M. Y. Ng, R. J. Sum, J. E. Bandow, D. Y. K. Chen, *Eur. J. Org. Chem.* **2011**, *2011*, 183-196.

[205] J. D. White, G. L. Bolton, A. P. Dantanarayana, C. M. J. Fox, R. N. Hiner, R. W. Jackson, K. Sakuma, U. S. Warrier, *J. Am. Chem. Soc.* **1995**, *117*, 1908-1939.

Therefore, we investigated protection of the tertiary hydroxy group at C7. Initially, we attempted to protect the carbinol of the dicarbonyl compound **2.114** with a labile TES (Table 2.6, entry 1) or TMS (entries 2 and 3) protecting group, which would allow for removal after ozonolysis and aldol cyclization using mild reaction conditions. Unfortunately, all silyl protection attempts on this substrate proceeded sluggishly and only the experiment using TMSI (2.5 equiv.) and HMDS (4 equiv.) in CH_2Cl_2 at 0°C formed the silyl ether, but also autoxidized the C1–C2 bond to the diene dione. This highly conjugated compound turned out to be an unsuitable substrate in the subsequent aldol cyclization due to its instability and high reactivity. Attempted installation of a THP or THF ether did either fail (entry 4) or show only low conversion to the desired compounds (entries 5 and 6).

Table 2.7: Selected conditions for the protection of the tertiary carbinol on the α-allylated α-hydroxyenone **2.80**.



entry	R	conditions[a]	observations
1	**Bn**	BnBr, NaH, TBAI, THF, rt	complex mixture[b]
2	**Bn**	BnBr, KHMDS, THF, –78°C to rt	complex mixture[b]
3	**Bn**	Bn-OPT, MgO, trifluorotoluene, 84°C, o.n.	dehydrated side product **2.123**[b]
4	**Bn**	$CCl_3C(=NH)OBn$ (4 equiv.), $Sc(OTf)_3$ (5 mol%), toluene, rt, 2 d	no conversion
5	**Bn**	$CCl_3C(=NH)OBn$ (4 equiv.), TfOH (5 mol%), CH_2Cl_2/CH (1:2), to rt	no conversion
6	**PMB**	$CCl_3C(=NH)OPMB$ (4 equiv.), $Sc(OTf)_3$ (5 mol%), CH_2Cl_2/CH (1:2), rt, o.n.	low conversion[b]
7	**PMB**	$CCl_3C(=NH)OPMB$ (4 equiv.), $Sc(OTf)_3$ (5 mol%), CH_2Cl_2/CH (1:2), 4 Å MS, rt, 1 h 30 min	60 % conversion[b]
8	**PMB**	$CCl_3C(=NH)OPMB$ (4 equiv.), $Yb(OTf)_3$ (5 mol%), CH_2Cl_2/CH (1:2), 4 Å MS, rt, 1 h 45 min	65 % **2.122**[c]

[a] Bn-OPT = 2-benzyloxy-1-methylpyridinium triflate; CH = cyclohexane; [b] monitored by ^{1}H NMR spectroscopy; [c] isolated yield after column chromatography.

In section 2.2.5, we presented a synthetic route leading to periconianone A using a benzyl protecting group for the tertiary carbinol. Therefore, we aimed at the installation of a benzyl (Bn) or para-methoxybenzyl (PMB) group for carbinol **2.80**. Selected conditions are summarized in Table 2.7. Basic conditions using BnBr, NaH and TBAI in THF resulted in a

complex mixture (entry 1).[206] Replacing NaH by KHMDS (entry 2), already successfully applied in the protection of tertiary hydroxyl groups,[207] did also not lead to the desired protected product **2.121**. Neutral conditions by using the Dudley reagent 2-benzyloxy-1-methylpyridinium triflate (Bn-OPT) at elevated temperature (84°C) triggered elimination of the tertiary hydroxyl group to form the dienone **2.123** (entry 3).[208] Under Lewis acidic conditions using $Sc(OTf)_3$ (entry 4) or in the presence of TfOH as Brønsted acid (entry 5) and the corresponding trichloroacetimidate,[209] benzylation did not take place; however, low conversion to the PMB-protected carbinol **2.122** was observed (entry 6). Applying the same conditions with addition of 4 Å molecular sieves as proton scavenger[210] and slow addition of the trichloroacetimidate improved the conversion to 60 %, as monitored by ^{1}H NMR spectroscopy (entry 7). With $Yb(OTf)_3$ as Lewis acid similar results with an isolated yield of 65 % for PMB-protected **2.122** (entry 8) were obtained.

A-ring modification by deprotection of the TBS group and oxidation of the secondary alcohol followed by ozonolysis gave the PMB-protected tricarbonyl compound **2.124** in 66 % yield over three steps. We were thus able to attempt the key aldol reaction to construct the C-ring. Applying the conditions used previously for the benzyl-protected tricarbonyl compound (DBU, CH_2Cl_2, O_2, rt) led to formation of a complex mixture (Table 2.8, entry 1). Using 20 mol% of the guanidine base TBD instead of DBU showed fast consumption of the aldehyde (30 min) at room temperature and formed a mixture of the dehydrogenated tricycle **2.125** and C1–C2 saturated tricycles **2.126** and **2.127** in a mixture of 1:1.4:2.3 (entry 2). When the same experiment was performed at –20°C, only low conversion was observed after stirring overnight (entry 3). However, when the amount of TBD was increased to two equivalents, **2.125**, **2.126** and **2.127** were formed in a ratio of 1:0.8:2.2 (entry 4). Using NaOMe in MeOH, conditions for the successful cyclization of methenylated tricarbonyl compound **2.68**, resulted in a complex mixture (entry 5). Under acidic conditions (HCl, acetone, rt), formation of a complex mixture was observed as well (entry 6). Organocatalytic aldol reactions using Hayashi-Jørgensen catalyst[211] showed no conversion at room temperature or at 40°C (entry 7). A major

[206] M. J. Di Grandi, C. A. Coburn, R. C. A. Isaacs, S. J. Danishefsky, *J. Org. Chem.* **1993**, *58*, 7728-7731.

[207] C. L. Hugelshofer, T. Magauer, *J. Am. Chem. Soc.* **2016**, *138*, 6420-6423.

[208] K. W. C. Poon, S. E. House, G. B. Dudley, *Synlett* **2005**, 3142-3144.

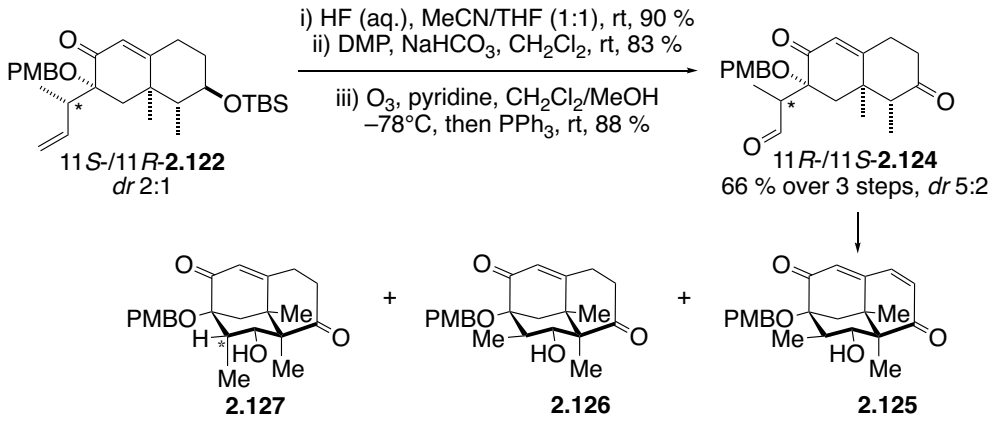
[209] P. Eckenberg, U. Groth, T. Huhn, N. Richter, C. Schmeck, *Tetrahedron* **1993**, *49*, 1619-1624; T. Iversen, D. R. Bundle, *J. Chem. Soc., Chem. Commun.* **1981**, 1240-1241.

[210] M. Adinolfi, G. Barone, A. Iadonisi, M. Schiattarella, *Tetrahedron Lett.* **2002**, *43*, 5573-5577.

[211] J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296-18304; Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215.

breakthrough for the cyclization reaction was found by treating tricarbonyl **2.124** with organophosphates as Brønsted acid catalysts:[212] although reactions using aqueous phosphoric acid (entry 8) showed no conversion, the chiral BINOL phosphate *R*-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (entry 9) or the achiral diphenyl phosphate (entry 10) both induced clean conversion to tricylces **2.126** and **2.127**, as monitored by ^{1}H NMR spectroscopy. Under the given reaction conditions, we found that the stereogenic center at C11 was not isomerized, as the ^{1}H NMR spectrum of the crude product showed formation of **2.126** and **2.127** in a ratio of 1:2; the same ratio as in the starting material.

Table 2.8: Synthesis of PMB-protected tricarbonyl compound **2.124** and aldol cyclization attempts.

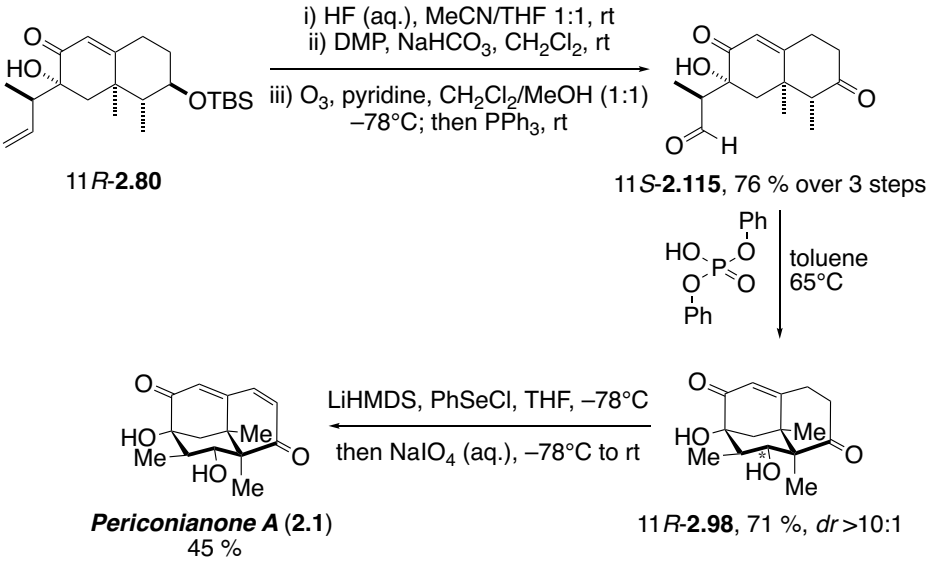


entry	conditions	2.125/2.126/2.127[a]	observations[a]
1	DBU (3 equiv.), CH_2Cl_2, O_2, rt, 3.5 h		complex mixture
2	TBD (20 mol%), THF, O_2, rt, 30 min	1:1.4:2.3	and other side products
3	TBD (20 mol%), THF, O_2, –20°C, o.n.		low conversion
4	TBD (2 equiv.), THF, O_2, –20°C, 2.5 h	1:0.8:2.2	and other side products
5	NaOMe (2 equiv.), MeOH, rt, 30 min		complex mixture
6	HCl (2 equiv.), acetone, rt, 30 min		complex mixture
7	Hayashi cat. (20 mol%), AcOH, CH_2Cl_2, rt, 2 h then 40°C, o.n.		no conversion
8	H_3PO_4 (20 % in H_2O), THF, 65°C, o.n.		no conversion
9	*R*-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (10 mol%), toluene, 65°C, o.n.	0:1:2	clean conversion to **2.126**/**2.127**
10	diphenyl phosphate, toluene, 65°C, 17 h	0:1:2	clean conversion to **2.126**/**2.127**

[a] ratio monitored by ^{1}H NMR spectroscopy.

[212] G. Pousse, F. L. Cavelier, L. Humphreys, J. Rouden, J. Blanchet, *Org. Lett.* **2010**, *12*, 3582-3585.

We were very pleased that under the same reaction conditions, the unprotected tricarbonyl compound **2.115** (*dr* 1:2) highly efficiently cyclizes to give the same 1:2 mixture (11*R*/11*S*) of aldol addition product **2.98**. Aiming at the preparation of pure 11*R*-**2.98**, diastereopure terminal olefin 11*R*-**2.80** was converted to the tricarbonyl compound 11*S*-**2.115** in 76 % yield over three steps. Aldol cyclization using the optimized reaction conditions (diphenyl phosphate, toluene, 65°C) gave the tricycle 11*R*-**2.98** in 71 % yield and with a diastereomeric ratio of >10:1, respective to C11 and C12.



Scheme 2.55: Synthesis of diastereopure tricarbonyl 11*S*-**2.115** and endgame in the synthesis of periconianone A (**2.1**) involving aldol cyclization to tricycle 11*R*-**2.98** using diphenyl phosphate and dehydrogenation of the C1–C2 bond.

With tricycle 11*R*-**2.98** in hand, we addressed the last transformation towards periconianone A (**2.1**) by introducing unsaturation at the C1–C2 bond. As already discussed in section 2.2.5.2, autoxidation by treating tricycle **2.98** with DBU or TBD did not bring about the desired oxidation. In section 2.2.3.4, dehydrogenation conditions have been screened for tricycle **2.70** lacking the C7 hydroxy group. Although not effective for the introduction of the C1=C2 unsaturation with substrate **2.70**, experiments using the Saegusa protocol [$Pd(TFA)_2$, O_2, DMSO, EtOAc, rt],[112] or hypervalent iodine reagents (iodic acid, cyclohexane, DMSO, 45°C)[148] have been tested on tricycle **2.98**. Unfortunately, both protocols led to decomposition of the starting material. Using DDQ (dioxane, 100°C), an effective reagent for installing α,β-unsaturation in steroidal ketones,[213] also led to decomposition. We were very pleased that α-selenylation followed by selenoxide elimination,[111] already successful for the

[213] D. Walker, J. D. Hiebert, *Chem. Rev.* **1967**, *67*, 153-195.

dehydrogenation of **2.70** (see section 2.2.3.4), facilitated conversion to periconianone A (**2.1**). After screening the reagent concentrations (LiHMDS and PhSeCl) and different oxidation reagents (H_2O_2, H_2O_2/pyridine, *m*-CPBA, O_3, $NaIO_4$), we found the best conditions by using LiHMDS (4 equiv.) and phenylselenyl chloride (2 equiv.) in THF at –78°C, before the reaction was quenched by addition of aqueous $NaIO_4$ and warming to room temperature. Work-up after the selenylation step prior to oxidation did not improve the yield of this reaction. Using Mukaiyama's reagent (*N*-tert-butylbenzenesulfinimidoyl chloride)[214] for the dehydrogenation in a one-pot manner with the aim to avoid the oxidation step did only form traces of the natural product **2.1**.

After purification by column chromatography, both the ^1H and ^{13}C NMR spectra of synthetic periconianone A (**2.1**) were in agreement with the reported spectra for the isolated material (Table 2.9 and Figure 2.3).[100]

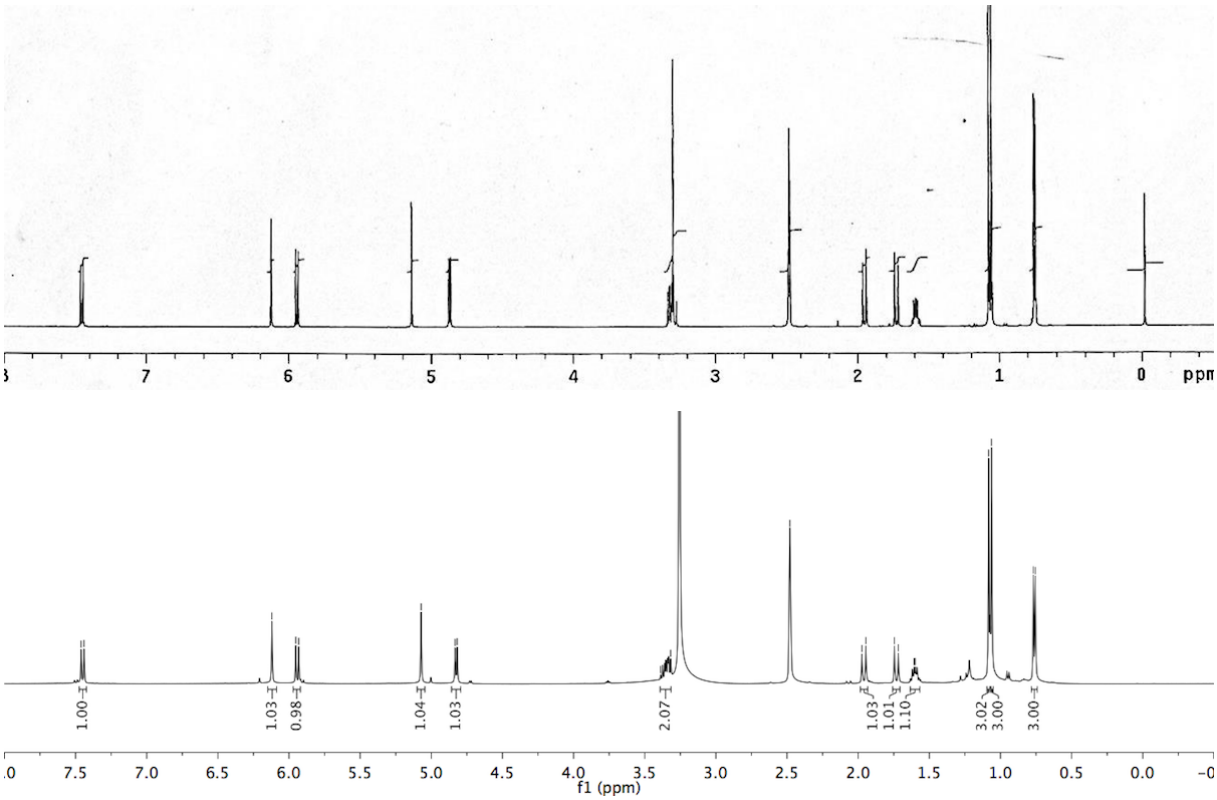
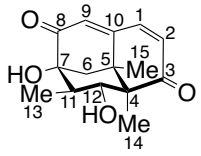


Figure 2.3: ^1H NMR (in DMSO-d_6) overlay of natural (top) and synthetic (bottom) periconianone A (**2.1**).

[214] T. Mukaiyama, J. Matsuo, H. Kitagawa, *Chem. Lett.* **2000**, 1250-1251.

Table 2.9: ^{1}H and ^{13}C NMR comparison for natural **2.1** and synthetic **2.1**.



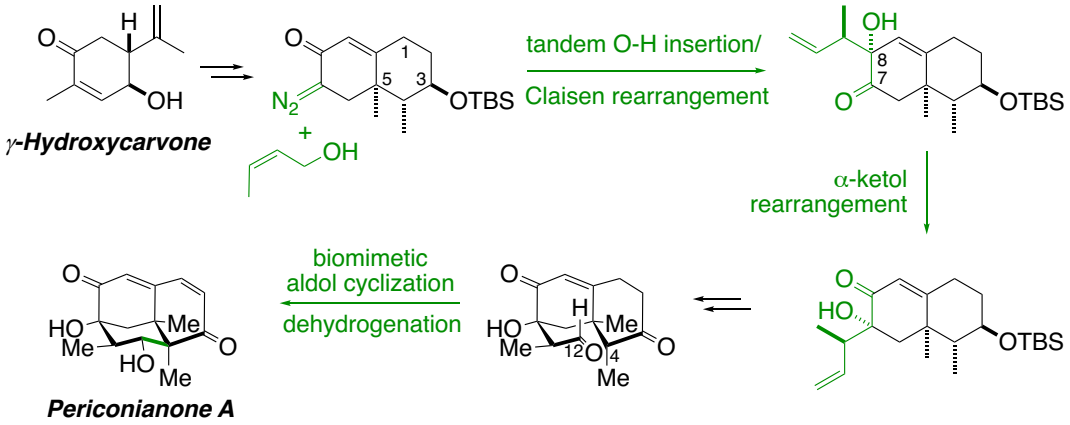
position	natural 2.1 δ_H lit.[a, b] (600 MHz, DMSO-d_6)	synthetic 2.1 δ_H this work[b] (500 MHz, DMSO-d_6)	natural 2.1 δ_C lit.[a] (150 MHz, DMSO-d_6)	synthetic 2.1 δ_C this work (126 MHz, DMSO-d_6)
1	7.45 (dd, 10.2, 1.2)	7.45 d (10.2)	142.3	142.3
2	5.94 (d, 10.2)	5.94 (d, 10.1)	128.8	128.8
3			199.9	199.9
4			56.0	56.0
5			44.8	44.9
6	1.95 (d, 13.8, Hβ)	1.96 (d, 13.8)	40.2	40.2
	1.73 (d, 13.8, Hα)	1.73 (d, 13.8)		
7			75.7	75.7
8			198.7	198.7
9	6.12 (s)	6.12 (s)	123.4	123.4
10			161.4	161.4
11	1.59 (m)	1.60 (dq, 10.1, 6.7)	44.8	44.9
12	3.32 (dd, 10.2, 7.2)	3.38 – 3.31 (m)	72.8	72.8
13	0.75 (d, 6.6)	0.76 (d, 6.7)	12.1	12.2
14	1.07 (s)	1.08 (s)	8.0	8.0
15	1.05 (s)	1.06 (s)	23.3	23.3
7-OH	5.14 (s)	5.07 (s)		
12-OH	4.87 (d, 7.2)	4.83 (d, 7.2)		

[a] See reference 100 for published NMR spectroscopic data of natural **2.1**. [b] coupling constants $J_{H\text{-}H}$ are given in parentheses (Hz).

2.3 Conclusion

In conclusion, the first enantioselective total synthesis of periconianone A was accomplished in 15 steps starting from known γ-hydroxy carvone (Scheme 2.56). The AB-ring system was efficiently constructed in six steps including a Criegee fragmentation to remove the isopropenyl moiety, a directing group used for the stereoselective installation of the substituents at C3, C4 and C5. Besides the key aldol transformation, the main challenge of the synthesis was the stereoselective elaboration of the C7 carbinol unit. Although present in diverse bioactive eremophilane-type natural products, there has so far been no synthetic strategy addressing the construction of this structural motif. After several synthetic proposals had been elaborated and

shown to be unsuccessful, we tackled this challenge by an early and stereoselective installation of this functional group before constructing the C-ring of periconianone A. The α-diazoketone derivative of the corresponding octalone was synthesized in two steps, and its transition metal carbene complex formed by reaction with a Rh(II) precursor reacted with (*Z*)-crotyl alcohol in an efficient tandem process of crotyl-*O*-insertion and spontaneous Claisen rearrangement. Treatment of the formed α-hydroxy ketone bearing the C8 carbinol unit with a simple and cost-efficient calcium salt then triggered the α-ketol rearrangement to shift the carbinol unit to the desired C7 position in a formal [2,3]-Wittig rearrangement.



Scheme 2.56: Key steps in the total synthesis of periconianone A.

After the A-ring as well as the allylic side chain had been modified by functional group interconversions, a postulated biogenetic aldol reaction furnished the complex cage-like tricyclic skeleton with high diastereoselectivity. Careful screening of reaction conditions enabled mimicking this late-stage aldol transformation without any protecting group for the sensitive β-hydroxy aldehyde, a motif that is prone to elimination or retro-aldol reactions. Additionally, aldol reactions catalyzed by organic phosphonic acids are rare and underexplored, and there are only few examples reported in literature. Our strategy sets the stage for the concise synthesis of other eremophilane-type natural products bearing a carbinol motif at C7 as well as the preparation of structurally diverse derivatives of periconianone A in order to find more potent neural anti-inflammatory active agents. SAR studies by preparation of periconianone A derivatives and biological testing of their ability to inhibit the LPS-induced NO production in mouse microglia BV2 cells are underway.

3 MICROSPHAEROPSISIN B AND C, PERICONIANONE C: TOTAL SYNTHESES AND BIOGENETIC RELATION

3.1 Introduction

Recently, the group of J. Dai reported an unusual furan-type *iso*-eremophilane, isolated from the endophytic fungus *Periconia* sp. F-31 and named periconianone C (**3.1**).[215] Extensive structure elucidation using 2D NMR spectroscopy indicated a linkage of the three-carbon moiety (usually bound at C7) to the C8 of the decalin core, a connectivity previously not reported for members of the furanoeremophilane-type sesquiterpene family (Figure 3.1).

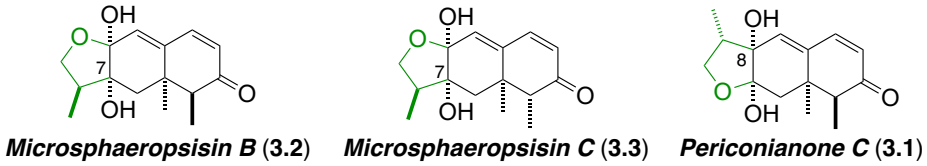
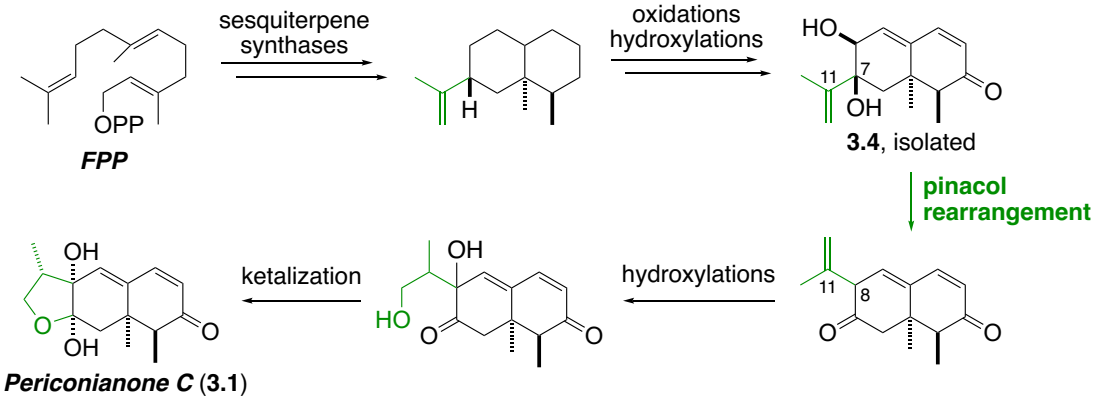


Figure 3.1: Chemical structures of microsphaeropsisins B (**3.2**) and C (**3.3**), and periconianone C (**3.1**).

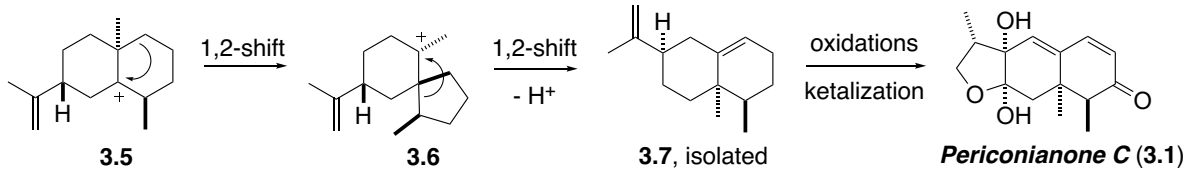
Additionally, the proposed structure was confirmed by single-crystal X-ray analysis and a biosynthetic pathway has been suggested (Scheme 3.1). It is assumed that after precursor **3.4**, bearing the usual C7–C11 linkage is formed by cyclization of FPP catalyzed by sesquiterpene synthases and subsequent oxidation events, a pinacol rearrangement might take place to shift the isopropenyl moiety from C7 to C8. Additional oxidation events would then form periconianone C (**3.1**) after ketalization. This biogenetic proposal is supported by the isolation of the putative precursor **3.4** from the same extracts of the fungus *Periconia* sp. F-31 as periconianone C (**3.1**).



Scheme 3.1: Proposed biosynthetic pathway to periconianone C (**3.1**) by J. Dai and co-workers.

[215] J. Liu, D. Zhang, M. Zhang, J. Zhao, R. Chen, N. Wang, D. Zhang, J. Dai, *J. Nat. Prod.* **2016**, *79*, 2229-2235.

A different biosynthetic proposal features an early rearrangement of the eudesmane-type precursor **3.5**: instead of methyl group migration to form the eremophilane skeleton, the C1–C10 bond might undergo a 1,2-alkyl shift to form the spiro intermediate **3.6**, whose C4–C5 bond can undergo another 1,2-shift to form the C8 isopropenylated decalin **3.7** (Scheme 3.2). This *iso*-eremophilane was isolated in small amounts from the roots of the South African *Helichrysum davyi* S. Moore by the group of F. Bohlmann.[216] Subsequent oxidation events on **3.7** might then lead to the formation of periconianone C. However, a pathway featuring spiro intermediates was ruled out for the biogenesis of C7 isopropenylated eremophilanes (see section 1.3) and as no other oxidized derivatives of C8–C11-connected eremophilanes have been described to date, this pathway appears less probable.

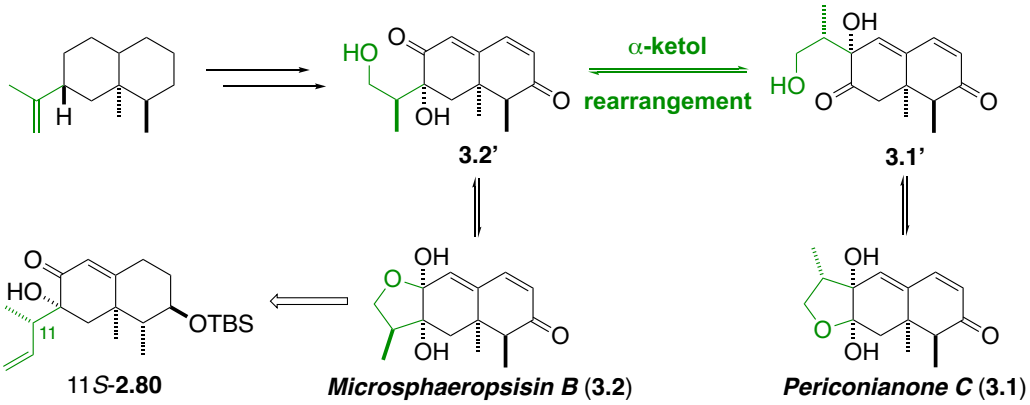


Scheme 3.2: Alternative hypothetical biosynthetic pathway to periconianone C (**3.1**) by an early rearrangement.

Only recently, two structurally very similar furan-type eremophilanes were isolated from co-cultivation of the endophytic fungus *Trichoderma* sp. 307 with the aquatic pathogenic bacterium *Acinetobacter johnsonii B2*, and named microsphaeropsisin B (**3.2**) and C (**3.3**) (Figure 3.1).[217] Except for the linkage of the furan moiety, the structure of microsphaeropsisin B is identical to the one of periconianone C. In the course of the total synthesis of periconianone A (see section 2), we discovered that bicyclic α-allylated α-hydroxyketones can undergo 1,2-shifts at positions C7 and C8. Based on these findings as well as the structural similarities of **3.1** and **3.2**, we suggested an alternative biogenesis for C8–C11-connected furanoeremophilanes by an equilibrium between the open forms of microsphaeropsisin B (**3.2'**) and periconianone C (**3.1'**) *via* an α-ketol rearrangement (Scheme 3.3).

[216] I. Jakupovic, T. Teetz, F. Bohlmann, *Phytochemistry* **1987**, *26*, 1841-1842.

[217] L. Zhang, S. Niaz, D. Khan, Z. Wang, Y. Zhu, H. Zhou, Y. Lin, J. Li, L. Liu, *Mar. Drugs* **2017**, *15*, 35.



Scheme 3.3: Our proposed biosynthetic pathway including microsphaeropsisin B (**3.2**) as a biogenetic precursor of periconianone C (**3.1**).

In order to investigate our proposed biogenetic proposal, we developed an efficient synthetic route to microsphaeropsisin B (**3.2**). Starting from 11*S*-α-alkylated α-hydroxyenone **2.80**, whose synthesis was elaborated in the course of the total synthesis of periconianone A (see section 2), we envisioned to modify the A-ring as well as the three-carbon side chain by a stepwise oxidation protocol to give access to microsphaeropsisin B (**3.2**). Having **3.2** at hand, we investigated the aforementioned transition of microsphaeropsisin B to periconianone C by an α-ketol rearrangement.

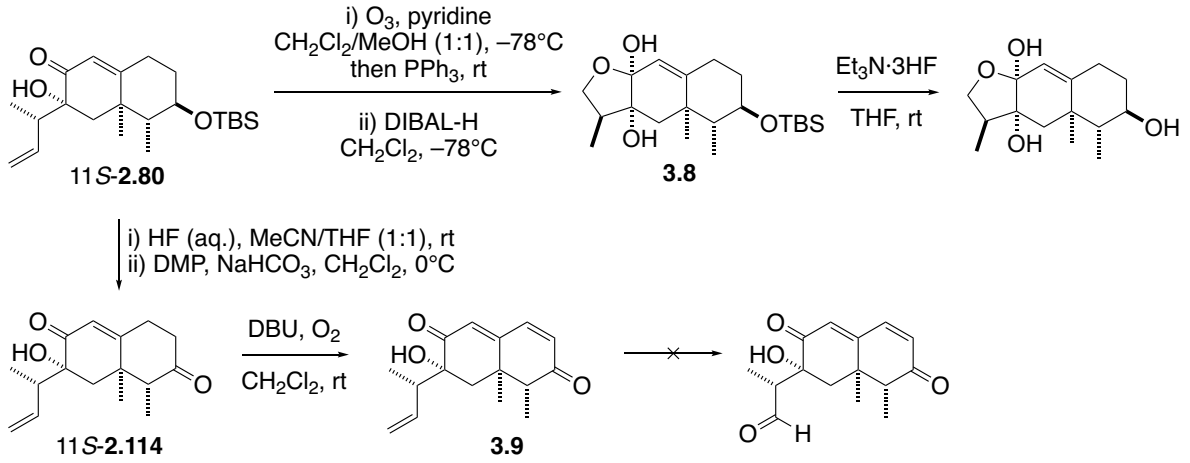
3.2 Results and Discussion

3.2.1 First Enantioselective Total Synthesis of Microsphaeropsisin B and C

For investigations on the transition of the 11*S*-isomer of α-alkylated α-hydroxyenone **2.80** to microsphaeropsisin B (**3.2**), different routes were elaborated.[218] The main challenge consisted in finding a suitable sequence for achieving the desired oxidation states on the functionalized positions, *i.e.* to optimize the order in which these reactions were to be carried out on the A-ring and on the side chain. Oxidative cleavage of the terminal double bond, followed by reduction of the formed aldehyde gave access to the furan-bearing compound **3.8** (Scheme 3.4). Although different fluoride sources were screened, deprotection of the TBS group was still low-yielding under optimized conditions using $Et_3N{\cdot}3HF$ in THF. Another approach consisted in fully oxidizing the A-ring prior to modification of the side chain: deprotection of the TBS group of 11*S*-**2.80** using HF in a MeCN/THF mixture was followed by DMP-mediated oxidation of the secondary alcohol to install the carbonyl moiety at C3 and gave 11*S*-**2.114** in 89 % yield over two steps. Unfortunately, dehydrogenation using DBU and O_2 in

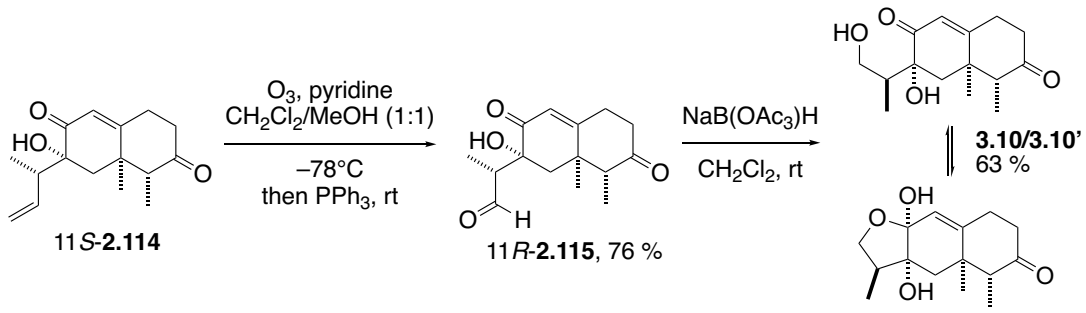
[218] N. Lardon, *Master Thesis* **2017**, Zurich.

CH_2Cl_2 was low-yielding and the formed diene dione **3.9** was found to be very unstable and unsuitable for the ensuing steps of the synthesis.



Scheme 3.4: A-ring and side chain modification attempts.

We therefore decided to use the approach outlined in Scheme 3.5: after installation of the carbonyl moiety at C3, a subsequent oxidative cleavage of the terminal double bond furnished aldehyde 11*R*-**2.115** in 76 % yield. Having this tricarbonyl-bearing substrate in hand, we addressed the selective reduction of the aldehyde at C12 without reducing the keto groups at C3 or C8. This transformation was identified as a key challenge and extensive screening was necessary to optimize the yield for the desired mono-reduced product **3.10**. Reactions with $NaBH_4$ were very low-yielding and also led to reduction of the carbonyl moiety at C3. The milder reducing agent $NBu_4B(OAc)_3H$ (prepared *in situ* form NBu_4BH_4 and AcOH)[219] gave only 18 % yield of the desired product **3.10**. Comparable results were obtained using $NMe_4B(OAc)_3H$:[220] at –20°C, a complex mixture was formed; at room temperature, traces of primary alcohol **3.10** could be detected.



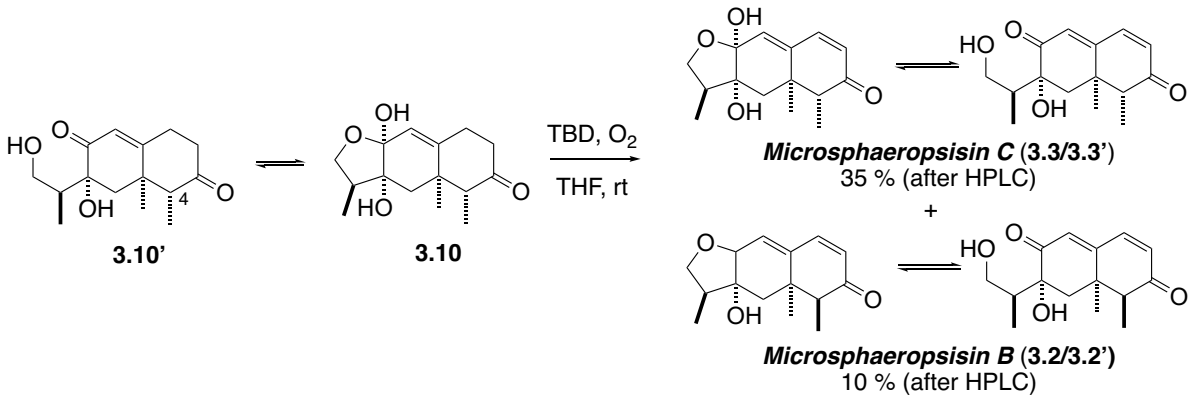
Scheme 3.5: Oxidative cleavage of 11*S*-**2.114** and reduction of the side chain in 11*R*-**2.115**.

[219] C. F. Nutaitis, G. W. Gribble, *Tetrahedron Lett.* **1983**, *24*, 4287-4290.

[220] S. A. Ramachandran, R. K. Kharul, S. Marque, P. Soucy, F. Jacques, R. Chênevert, P. Deslongchamps, *J. Org. Chem.* **2006**, *71*, 6149-6156.

After screening different reaction temperatures and various concentrations of the reducing agent DIBAL-H, we found superior conditions at –88°C to –78°C by using 1.5 equivalents of DIBAL-H to yield a mixture of 28 % of the desired product, 12 % of doubly reduced (C12 and C3) compound and 11 % of starting material. Testing other reducing agents for this transformation, we obtained the best result by adding three equivalents of $NaB(OAc)_3H$ to a solution of the aldehyde 11*R*-**2.115** in CH_2Cl_2 to give 63 % of the desired mono-reduced compound **3.10**.[221]

With intermediate **3.10** in hand, we started to investigate the final dehydrogenation step to microsphaeropsisin B (**3.2**). When the aldol reaction for construction of the C-ring in the total synthesis of periconianone A (**2.1**) had been carried out in the presence of DBU or TBD, this reaction had been accompanied by oxidation of the C1–C2 bond of the Bn- (**2.96**) or PMB-protected (**2.124**) tricarbonyl compounds to give the desired diene dione function prior to cyclization (see section 2.2.5.2). We applied the same reaction conditions to substrate **3.10** with the aim not only to dehydrogenate the C1–C2 bond, but also to epimerize the stereogenic center in α-position to the carbonyl moiety at C4 to form both microsphaeropsisin B (**3.2**) and C (**3.3**). Initial attempts by using DBU in CH_2Cl_2 only led to trace amounts of the desired compounds. However, a significant increase in yield for both natural products was achieved by applying TBD.



Scheme 3.6. Dehydrogenation and C4 epimerization to complete the total synthesis of microsphaeropsisin B (**3.2**) and C (**3.3**).

After work-up, analysis of the ^{1}H NMR spectra of the crude reaction mixture still indicated the presence of unidentified side products. Therefore, we monitored this transformation by means of ^{1}H NMR spectroscopy, aiming to gain insights into the mechanism of this reaction. Briefly, after 15 minutes, the formation of an unknown intermediate was

[221] A. Orue, U. Uria, E. Reyes, L. Carrillo, J. L. Vicario, *Angew. Chem. Int. Ed.* **2015**, *54*, 3043-3046.

observed, which disappeared with prolonged reaction time. Only traces of this intermediate could be detected after four hours, which prompted us to extend the reaction time from 30 minutes to five hours. This modification did not only give better yields, it also proved to be the key for the successful isolation of pure microsphaeropsisin B (**3.2**), after attempts to separate this intermediate from **3.2** had been unsuccessful using column chromatography or RP-HPLC.

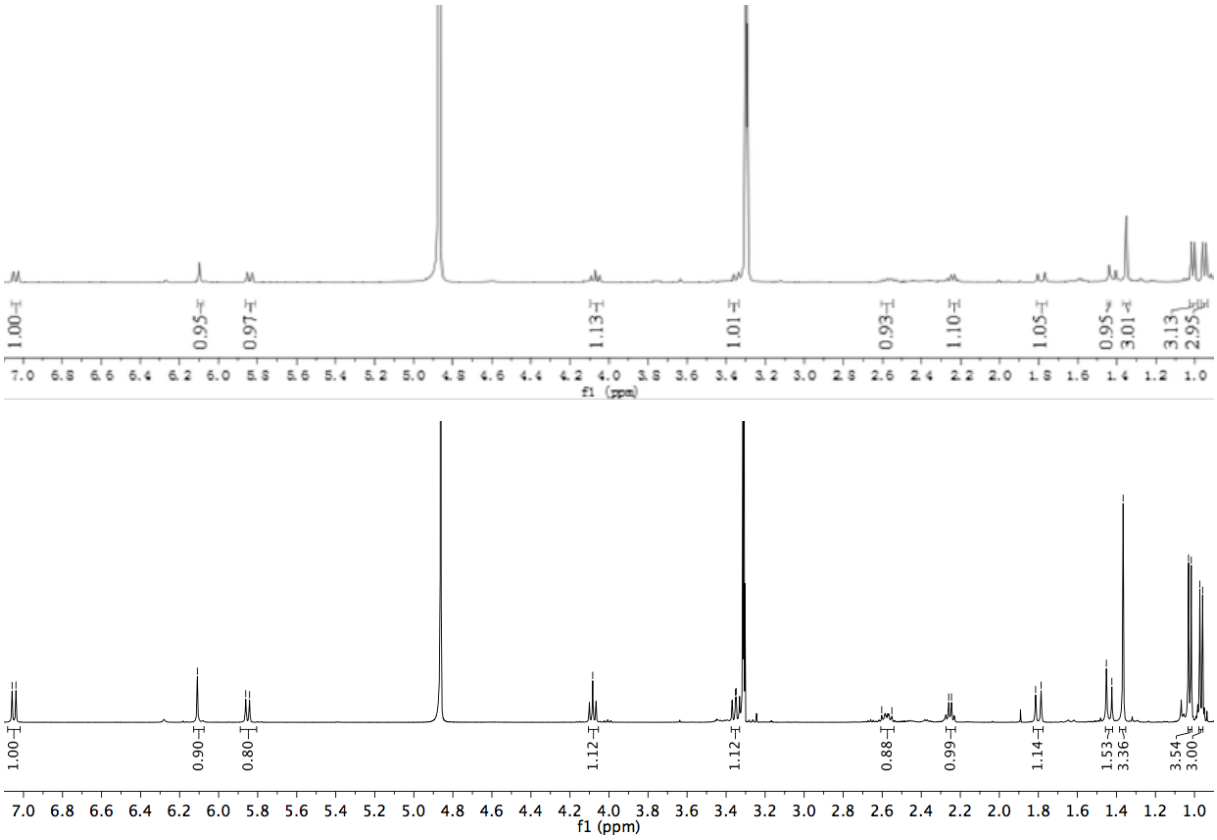


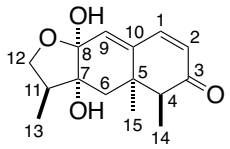
Figure 3.2: ^{1}H NMR spectra (in MeOD-d_4) of natural (top)[217] and synthetic (bottom) microsphaeropsisin B (**3.2**).

Mechanistically, we suggest the intermediacy of a peroxide species in this transformation, which forms **3.2** and **3.3** after elimination of H_2O_2. This assumption is based on literature precedents that describe transformations of steroidal ketones into their corresponding hydroperoxy ketones in the presence of oxygen under basic conditions, and the isolation and characterization of such intermediates.[154] In order to examine if the dehydrogenation of **3.10** to **3.2** and **3.3** might proceed *via* a similar pathway, we measured the reaction mixture's peroxide concentration: indeed, the presence of H_2O_2 was indicated both after 15 minutes and 2.5 hours, and increased with prolonged reaction time. In order to rule out the oxidation of THF in this reaction mixture,[222] we performed a test reaction in the absence of substrate **3.10**: both after 15 minutes and 2.5 hours no peroxide formation was monitored in pure THF, confirming the

[222] H. L. Jackson, W. B. McCormack, C. S. Rondestvedt, K. C. Smeltz, I. E. Viele, *J. Chem. Educ.* **1970**, *47*, A175.

starting material to be involved in this process. After separation by preparative HPLC, we obtained microsphaeropsisin C (**3.3**) in 35 %, and microsphaeropsisin B (**3.2**) in 10 % yield. The ^{1}H and ^{13}C NMR spectra of the synthesized compounds were in agreement with those reported in literature for the isolated natural products (Table 3.1 and Table 3.2).[217] However, we identified additional minor signals in the ^{1}H (Figure 3.2 and Figure 3.3) as well as ^{13}C NMR spectra. These signals are hardly visible in the ^{1}H NMR spectra of the isolated compounds and no structural assignment had been performed by L. Zhang *et al*.[217] After extensive structural elucidation using 2D NMR, we could assign those minor signals to the open forms of the corresponding natural products (not shown in Table 3.1 and Table 3.2, see experimental section 6.4), which are in equilibrium with their furan-type isomers (Scheme 3.6).

Table 3.1: ^{1}H and ^{13}C NMR data of natural and synthetic microsphaeropsisin B (**3.2**).



position	natural 3.2 δ_H lit.[a, b] (400 MHz, MeOD-d_4)	synthetic 3.2 δ_H this work[b] (500 MHz, MeOD-d_4)	natural 3.2 δ_C lit.[a] (100 MHz, MeOD-d_4)	synthetic 3.2 δ_C this work (126 MHz, MeOD-d_4)
1	7.04 (d, 9.8)	7.05 (d, 9.8)	146.6	146.6
2	5.84 (d, 9.8)	5.85 (d, 9.8)	126.3	126.3
3			206.8	206.8
4	2.24 (q, 7.3)	2.25 (q, 7.2)	55.0	55.0
5			39.9	39.9
6	1.79 (d, 14.1)	1.80 (d, 14.0)	34.6	34.6
	1.44 (d, 14.1)	1.44 (d, 14.1)		
7			77.8	77.8
8			100.5	100.5
9	6.10 (s)	6.11 (s)	135.3	135.3
10			139.4	139.4
11	2.58 (ddq, 8.3, 7.2, 6.4)	2.60 – 2.55 (m)	43.9	43.8
12	4.07 (dd, 8.8, 8.3)	4.08 (t, 8.5)	71.8	71.8
	3.34 (dd, 8.8, 6.4)	3.35 (dd, 10.5, 8.5)		
13	1.01 (d, 7.2)	1.02 (d, 7.0)	9.2	9.2
14	0.95 (d, 7.3)	0.97 (d, 7.1)	14.8	14.8
15	1.35 (s)	1.37 (s)	28.0	28.0

[a] See reference 217 for published NMR spectroscopic data of natural **3.2**. [b] coupling constants $J_{H\text{-}H}$ are given in parentheses (Hz).

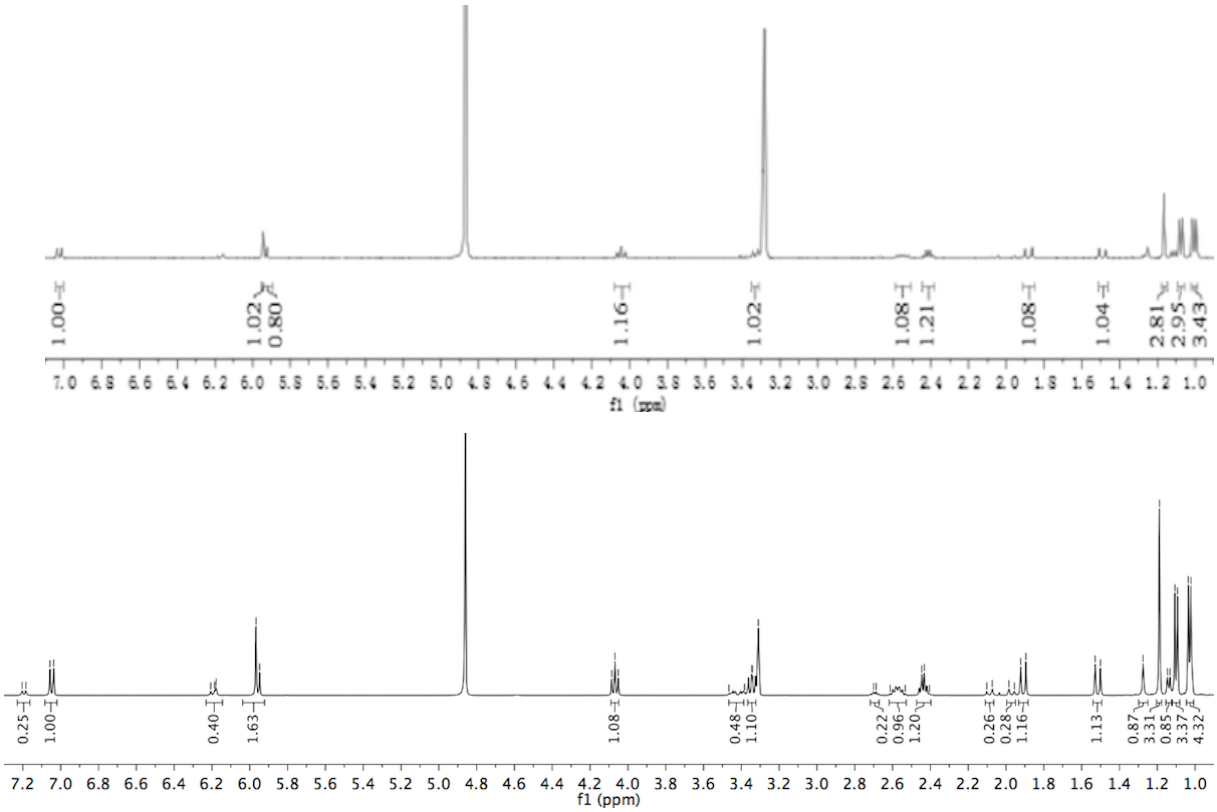
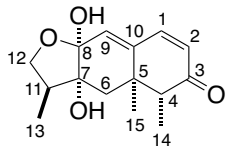


Figure 3.3: ^{1}H NMR spectra (in MeOD-d_4) of natural (top)[217] and synthetic (bottom) microsphaeropsisin C (**3.3**).

Optical rotation values of both synthesized natural products were measured and compared to the ones reported in literature for the isolated material in order to confirm their absolute configuration to be identical: the measured value of $[\alpha]_D^{25} = -20.2°$ (c = 0.60, MeOH) for microsphaeropsisin B (**3.2**) was in agreement with the one reported in literature ($[\alpha]_D^{20} = -16.0°$ (c = 0.10, MeOH)); however, a significant discrepancy was observed for microsphaeropsisin C (**3.3**) with an optical rotation value of $[\alpha]_D^{24} = +67.0°$ (c = 0.48, MeOH) for the synthesized and a reported value of $[\alpha]_D^{20} = -124.0°$ (c = 0.025, MeOH) for the isolated material. In order to prove the isolated natural and synthetic **3.3** to be identical, we measured a CD spectrum of synthesized microsphaeropsisin C, which was in agreement with the one reported in literature (Figure 3.4).[217]

Table 3.2: ^{1}H and ^{13}C NMR data of natural and synthetic microsphaeropsisin C (**3.3**).



position	natural 3.3 δ_H lit.[a, b] (400 MHz, MeOD-d_4)	synthetic 3.3 δ_H this work[b] (500 MHz, MeOD-d_4)	natural 3.3 δ_C lit.[a] (100 MHz, MeOD-d_4)	synthetic 3.3 δ_C this work (126 MHz, MeOD-d_4)
1	7.01 (d, 9.8)	7.05 (d, 9.8)	146.1	146.1
2	5.93 (d, 9.8)	5.96 (d, 9.4)	128.4	128.4
3			203.4	203.4
4	2.40 (q, 6.9)	2.44 (q, 6.8)	54.4	54.4
5			40.4	40.4
6	1.87 (d, 14.0)	1.91 (d, 13.9)	38.9	38.9
	1.51 (d, 14.0)	1.51 (d, 14.0)		
7			77.6	77.6
8			100.3	100.3
9	5.94 (s)	5.97 (s)	132.2	132.2
10			142.4	142.4
11	2.54 (ddq, 7.8, 6.9, 6.4)	2.61 – 2.53 (m)	43.9	43.9
12	4.04 (dd, 8.3, 7.8)	4.07 (t, 8.5)	71.6	71.6
	3.31 (dd, 8.3, 6.4)	3.34 (dd, 10.6, 8.5)		
13	1.01 (d, 6.9)	1.03 (d, 7.0)	9.2	9.2
14	1.08 (d, 6.9)	1.10 (d, 6.8)	7.5	7.5
15	1.16 (s)	1.19 (s)	20.9	20.9

[a] See reference 217 for published NMR spectroscopic data of natural **3.3**. [b] coupling constants $J_{H\text{-}H}$ are given in parentheses (Hz).

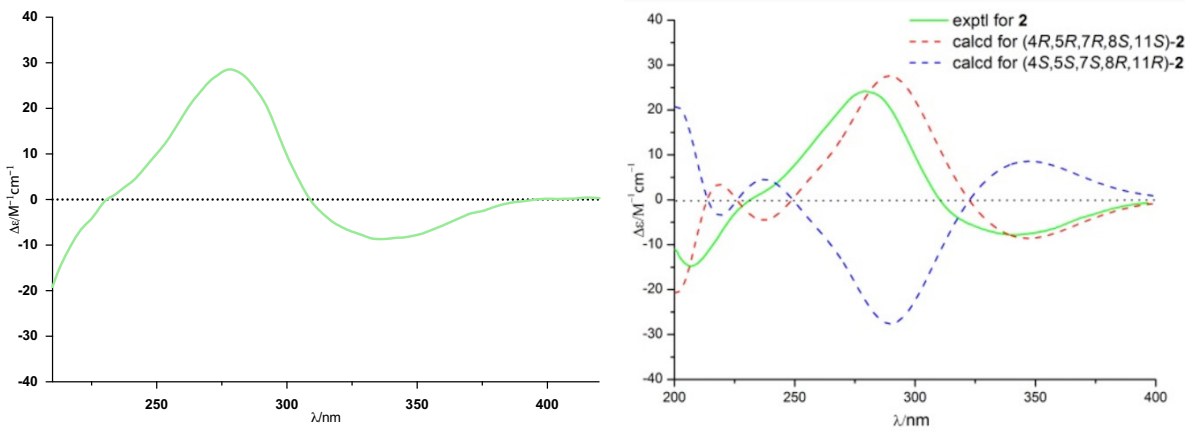
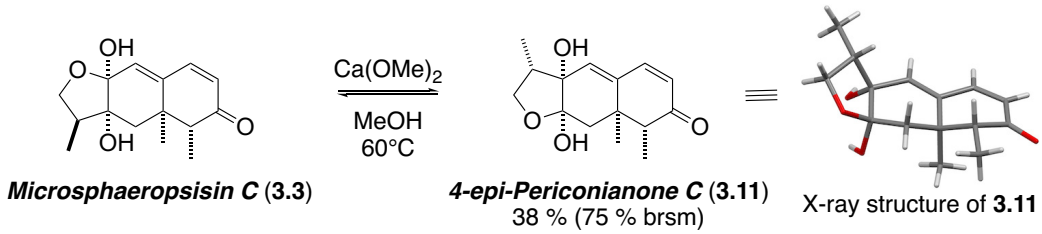


Figure 3.4: CD spectrum of synthetic microsphaeropsisin C (**3.3**) in MeOH (left), reported CD spectrum of isolated **3.3** in MeOH (right).[217]

3.2.2 α-Ketol Rearrangement of Microsphaeropsisin B and C to Periconianone C and 4-*epi*-Periconianone C

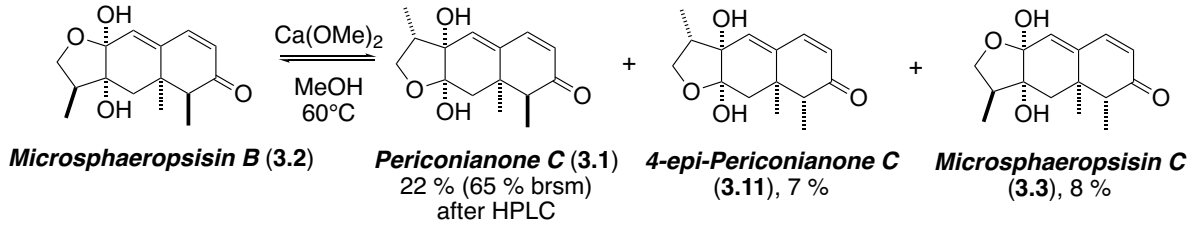
With microsphaeropsisin B (**3.2**) and C (**3.3**) in hand, the stage was set to investigate the hypothesis of a biomimetic α-ketol rearrangement for the transition of both natural products into their respective rearranged C8–C11-connected regioisomers. Our studies commenced with the transposition of **3.3**. Unfortunately, the best conditions for triggering the reaction of **2.84** to **2.80** ($Ca(OMe)_2$, MeOH, rt) did not bring about the desired conversion of **3.3** to **3.11**, as monitored by ^{1}H NMR spectroscopy of the crude reaction mixture. Therefore, the reaction mixture was heated to 60°C and we were very pleased to observe that a new compound was formed and identified as the 4-*epi*-isomer of periconianone C after isolation and careful structural elucidation by 2D NMR spectroscopy. Additionally, the structure of **3.11** was confirmed by single-crystal X-ray analysis (Scheme 3.7). Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy mainly showed the product **3.11** and starting material **3.3** with hardly any side products. After purification by flash column chromatography, 4-*epi*-periconianone C and microsphaeropsisin C were isolated in a combined yield of 75 % in almost equivalent amount.



Scheme 3.7: Transposition of microsphaeropsisin C (**3.3**) to 4-*epi*-periconianone C (**3.11**) *via* an α-ketol rearrangement.

The same reaction conditions ($Ca(OMe)_2$, MeOH, 60°C) were applied to microsphaeropsisin B (**3.2**) with the aim to trigger the α-ketol rearrangement to periconianone C (**3.1**). Fortunately, the desired natural product **3.1** was observed along with remaining starting material **3.2** by ^{1}H NMR analysis of the crude mixture (Scheme 3.8). Additionally, during the course of the reaction, the basic conditions triggered partial epimerization at C4 to form microsphaeropsisin C (**3.3**) as well as 4-*epi*-periconianone C (**3.11**). After no epimerization had been observed for the reaction using microsphaeropsisin C as starting material, we assume a higher stability for the compounds with *cis*-configuration (**3.3** and **3.11**) of the methyl groups at C4 and C5, compared to those with *trans*-configuration (**3.1** and **3.2**). This hypothesis is

further supported by the fact that higher concentrations of **3.3**, compared to **3.2**, were found in the fungal extracts.



Scheme 3.8: Transposition of microsphaeropsisin B (**3.2**) to periconianone C (**3.1**) *via* an α-ketol rearrangement.

Separation of the crude reaction mixture containing the four known isomers was found to be challenging: by column chromatography we were only able to separate the more apolar 4-*epi*-periconianone C (**3.11**) from the other three compounds **3.1**, **3.2** and **3.3**. Therefore, conditions for separation by reversed-phase HPLC have been screened and a reasonable separation for microsphaeropsisin B (43 %) and C (8 %), as well as for periconianone C (22 %) and 4-*epi*-periconianone C (7 %) was achieved using an isocratic solvent system of 20 % MeCN in water (Figure 3.5).

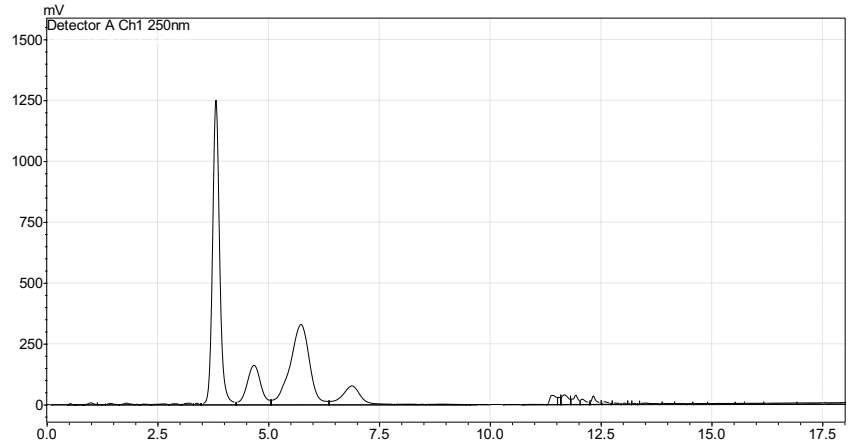
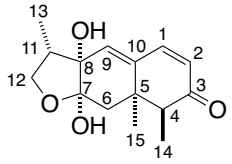


Figure 3.5: Semi-preparative RP-HPLC chromatogram of **3.2**, **3.3**, **3.1** and **3.11** (solvent: 20 % MeCN in water, isocratic).

The ^{1}H and ^{13}C NMR spectra of synthesized periconianone C (**3.1**) were in agreement with the spectra reported in literature for the isolated material (Table 3.3),[215] and both the opened and closed structures of **3.1** were observed in the ^{1}H NMR spectrum (Figure 3.6). The optical rotation values for synthesized ($[\alpha]_D^{22}$ = –53.8° (c = 0.19, MeOH)) and natural material ($[\alpha]_D^{22}$ = –45.5° (c = 0.11, MeOH)) do not significantly differ.[215]

Table 3.3: ^{1}H and ^{13}C NMR data of natural and synthetic periconianone C (**3.1**).



position	natural 3.1 δ_H lit.[a, b] (600 MHz, DMSO-d_6)	synthetic 3.1 δ_H this work[b] (500 MHz, DMSO-d_6)	natural 3.1 δ_C lit.[a] (150 MHz, DMSO-d_6)	synthetic 3.1 δ_C this work (126 MHz, DMSO-d_6)
1	7.06 (d, 9.6)	7.06 (d, 9.7)	144.6	144.6
2	5.77 (d, 9.6)	5.77 (d, 9.7)	124.2	124.2
3			203.0	203.0
4	2.07 (q, 6.6)	2.07 (q, 7.2)	52.4	52.5
5			40.0	39.7
6	1.95 (d, 13.8)	1.95 (d, 13.9)	41.7	41.7
	1.65 (d, 13.8)	1.65 (d, 13.8)		
7			103.0	103.0
8			76.1	76.1
9	6.14 (s)	6.13 (s)	136.8	136.8
10			136.7	136.7
11	2.16 (m)	2.22 – 2.12 (m)	44.6	44.6
12	3.73 (dd, 7.8, 7.8)	3.73 (t, 7.4)	70.0	70.0
	3.53 (dd, 7.8, 11.4)	3.53 (dd, 11.1, 7.4)		
13	0.95 (d, 6.6)	0.95 (d, 6.6)	9.1	9.1
14	0.87 (d, 6.6)	0.87 (d, 7.1)	14.2	14.2
15	1.19 (s)	1.18 (s)	26.1	26.1
7-OH		5.61		
8-OH		5.23		

[a] See reference 215 for published NMR spectroscopic data of natural **3.1**. [b] coupling constants $J_{H\text{-}H}$ are given in parentheses (Hz).

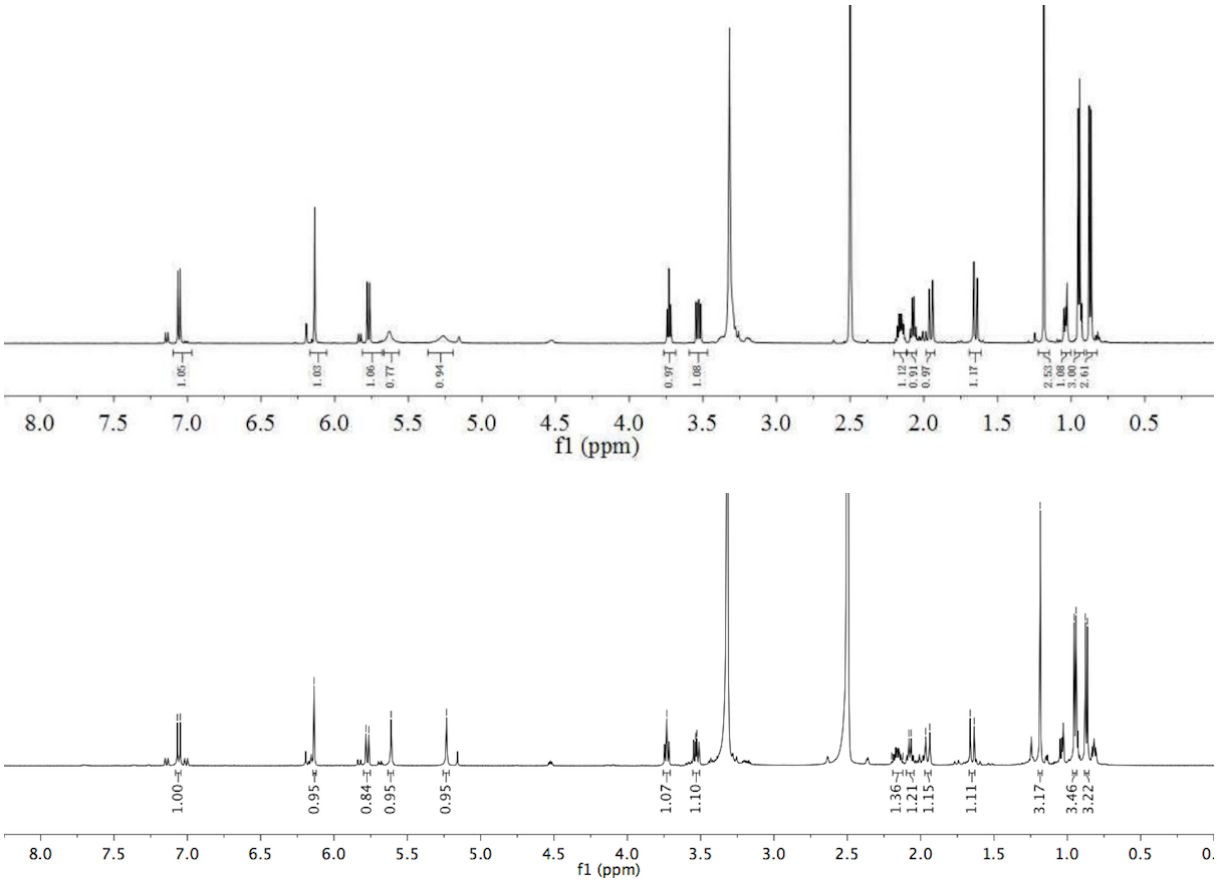


Figure 3.6: ^{1}H NMR spectra (in DMSO-d_6) of natural (top) and synthetic (bottom) periconianone C (**3.1**).[215]

3.3 Conclusion

In conclusion, the first enantioselective total syntheses of microsphaeropsisin B and C in 15 steps from known γ-hydroxy carvone are presented. The tandem OH-insertion/[3,3] rearrangement as well as the α-ketol rearrangement, both key reactions developed in the course of the total synthesis of periconianone A, have been successfully incorporated into our synthetic route for the synthesis of the desired 11*S*-isomer of α-allylated α-hydroxy enone **2.80**. For the last five synthetic transformations, selective reduction of the aldehyde in the presence of two other carbonyl moieties was identified as an exigent challenge. After careful screening of reaction conditions, we achieved the desired mono-reduction with high chemoselectivity and without overreduction of the substrate. Unusual autoxidation conditions using a guanidine base and molecular oxygen did not only lead to dehydrogenation of the C1–C2 bond to form the desired diene dione, but also to epimerization of the C4 position forming both C7–C11-connected natural product stereoisomers. After minor modification of our protocol for the α-ketol rearrangement, we were successful to bring about the rearrangement of both natural products microsphaeropsisin B and C into their regioisomers periconianone C and 4-*epi*-periconianone C by heating the substrates with calcium methoxide in MeOH. These findings strongly support our biogenetic hypothesis of microsphaeropsisin B being a biosynthetic precursor of periconianone C, and hint at the occurrence of other eremophilane-type terpenoids bearing a C8–C11 linkage.

4 TOTAL SYNTHESES OF GUIGNARDEREMOPHILANE C AND D

4.1 Introduction

Except for C5, all carbons in eremophilanes are known to be accessible for oxidation, with hydroxylation often taking place at C1, C3, C7 and/or C12. However, C1,C2,C3-trihydroxylated eremophilanes are rare: besides the two target compounds, only four such natural products have been described to date, *viz.* ligumacrophyllatin,[223] sporogen AO-2,[224] 1β,8β-dihydroxy-2β,3α-diangeloyloxyeremophil-7(11)-en-8α(12)-olide,[225] and guignard-eremophilane F[226] (Figure 4.1). The former is characterized by an all α–configuration of the three hydroxy groups (1α,2α,3α); the second by a 1α,2β,3α-configuration; the third by a 1β,2β,3α-configuration; and the latter as a stereoisomer of guignarderemophilane C by a 1β,2α,3α-configuration.

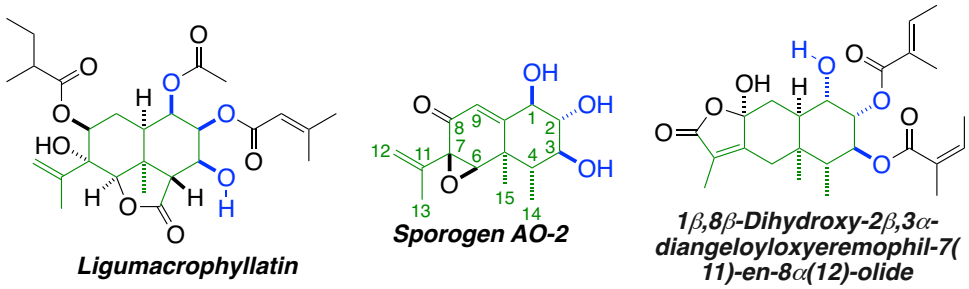


Figure 4.1: Eremophilane sesquiterpenes containing a 1,2,3-trihydroxylated A-ring.

Neither of these compounds have been synthesized yet and there is no reported preparative strategy addressing this unusual trihydroxylated A-ring motif. Recently, two natural products with a 1α,2β,3β-trihydroxylated scaffold have been isolated for the first time from the fungus *Guignardia mangiferae*, and named guignarderemophilanes C (**4.1**) and D (**4.2**).[227] The fungus *Guignardia mangiferae* is an endosymbiont of plants such as *Gelsemium elegans*, whose extracts are used in traditional Chinese medicine as nervous relaxant and for the treatment of pain.[228] Both eremophilanes showed neural anti-inflammatory activity by inhibiting the LPS-induced NO production in BV2 cells with IC_{50} values of 6.4 and 4.2 μM, respectively.[227]

[223] B. Fu, Q. X. Zhu, X. P. Yang, Z. J. Jia, *Pharmazie* **2002**, *57*, 275-278.

[224] Y.-B. Zeng, S.-S. Li, W.-L. Mei, W.-H. Dong, K.-M. Li, H.-F. Dai, *J. Asian Nat. Prod. Res.* **2015**, *17*, 280-284.

[225] E. W. Li, J. Pan, K. Gao, Z. J. Jia, *Planta Med.* **2005**, *71*, 1140-1144.

[226] Y. Zhou, Y.-H. Li, H.-B. Yu, X.-Y. Liu, X.-L. Lu, B.-H. Jiao, *J. Asian Nat. Prod. Res.* **2017**, 1-8.

[227] Y. Liu, Y. Li, J. Qu, S. Ma, C. Zang, Y. Zhang, S. Yu, *J. Nat. Prod.* **2015**, *78*, 2149-2154.

[228] V. Dutt, S. Thakur, V. J. Dhar, A. Sharma, *Pharmacogn. Rev.* **2010**, *4*, 185-194.

Besides periconianone A (see section 2.1), guignarderemophilanes C and D and their derivatives may be potential lead candidates for developing treatment options for neuro-degenerative diseases, too.

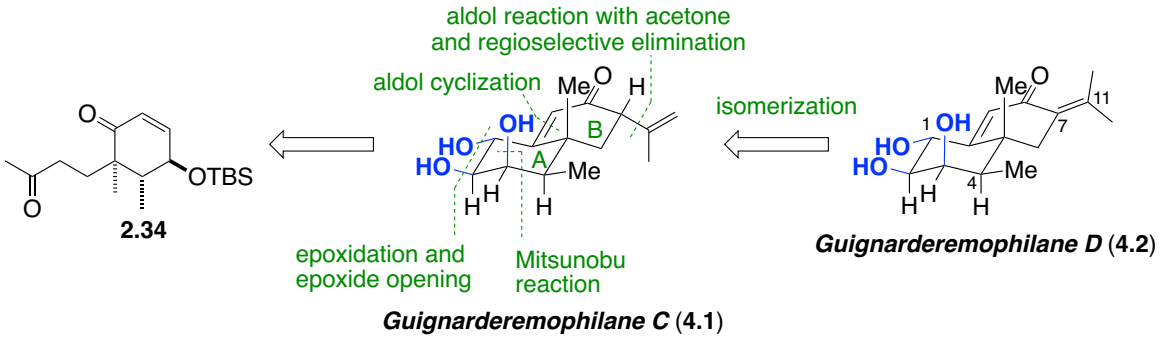


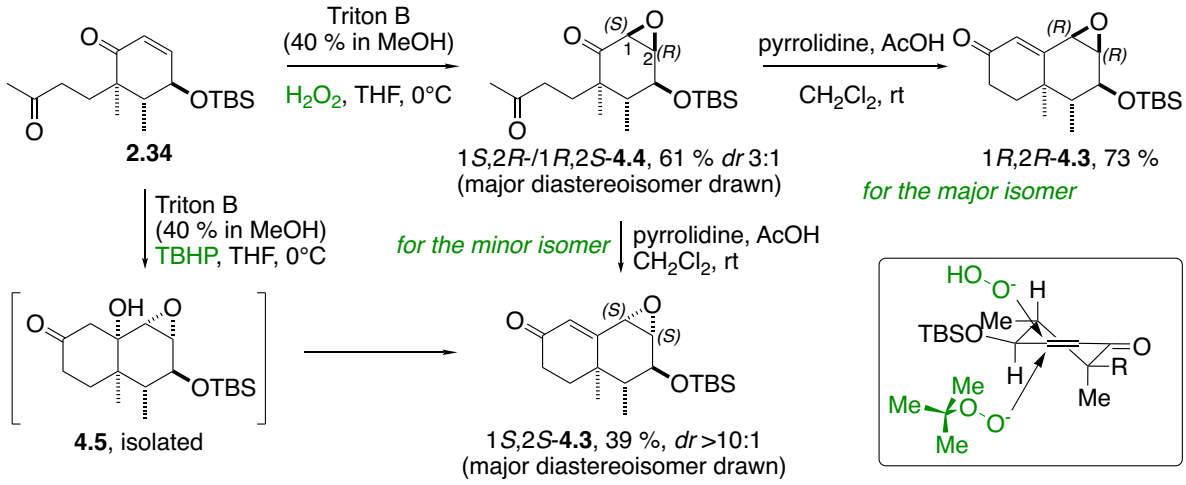
Figure 4.2. Retrosynthetic analysis of guignarderemophilanes C (**4.1**) and D (**4.2**), starting from the known enone **2.34**.

Besides the unusual 1,2,3-trihydroxylated scaffold, another striking structural feature of both eremophilane sesquiterpenoids is the presence of five contiguous stereogenic centers in the six-membered A-ring, one of which is quaternary. Guignarderemophilane C contains an additional stereogenic center (C7) connected to an isopropenyl moiety with unsaturation in β,γ position of the carbonyl group, which is prone to isomerize to the α,β-unsaturated ketone, as in guignarderemophilane D. From a retrosynthetic perspective, we envisioned to use cyclo-hexanone derivative **2.34**, whose synthesis has been elaborated in the course of the total synthesis of periconianone A (see section 2.2.1.3). As a first challenge, we addressed the stereo-selective installation of the aforementioned three hydroxy groups. To this end, we envisioned inversion of the stereocenter at C3 by Mitsunobu reaction of cyclohexanone derivative **2.34**, as well as a diastereoselective epoxidation and regioselective epoxide opening sequence to install the C1 and C2 hydroxy groups. Functionalization at C7 to install the three-carbon unit for completion of the 15-carbon skeleton was envisioned by an aldol addition of acetone, followed by regioselective dehydration.

4.2 Results and Discussion

We had at first envisioned the synthesis to commence by epoxidation of the C1=C2 double bond of enone **2.34**, followed by an aldol condensation to form the octalone core **4.3**

(Scheme 4.1).[229] While screening conditions for the epoxidation, we found diverging diastereoselectivities for different peroxide sources: with hydrogen peroxide,[230] epoxidation on the same face as the OTBS group in the A-ring was observed and we isolated epoxy ketones 1*S*,2*R*- and 1*R*,2*S*-**4.4** with a *dr* of 3:1. Using *tert*-butyl hydrogen peroxide, the epoxidation exclusively took place (*dr* > 10:1) on the opposite face with respect to the OTBS group. Observations for similar substrates with comparable stereochemical outcome have already been described in literature.[231] Although the obtained selectivities cannot be fully explained based on steric or stereoelectronic effects or both, it might be reasonable to argue that attack of the sterically more demanding *tert*-butyl hydrogen peroxide preferably takes place from the less shielded face of the six-membered ring at C2 of **2.34** with the OTBS group in a pseudoequatorial position. However, applying the described conditions for the latter reaction, instead of the epoxy ketone, we observed spontaneous closure of the B-ring to form the octalone 1*S*,2*S*-**4.3** (Scheme 4.1).



Scheme 4.1: Epoxidation of enone **2.34** and tandem epoxidation/aldol condensation approach.

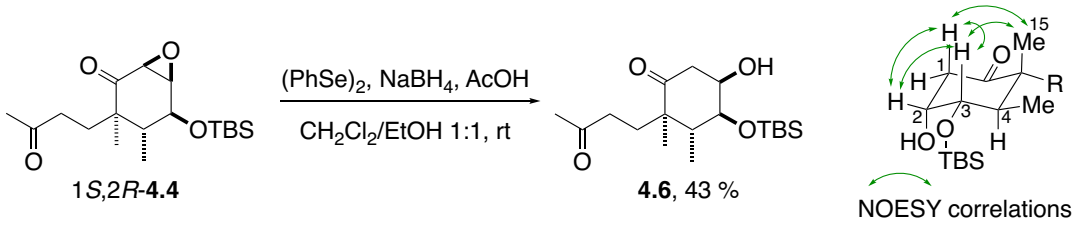
To the best of our knowledge, this is the first reported example of a tandem epoxidation–aldol condensation sequence. After work-up of the reaction mixture, the ^{1}H NMR spectrum of the crude product indicated formation of octalone 1*S*,2*S*-**4.3** and an unknown compound in a ratio of 4:1. When the reaction time was decreased from five hours to one hour, the ratio of the two products increased to 2:3 in favor of the unknown compound. This byproduct was identified to be the bicyclic γ,δ-epoxy β-hydroxy ketone **4.5** by isolation and structure elucidation based on 2D NMR spectra. Therefore, we hypothesize the epoxidation to take place prior to the aldol

[229] A. Ilazi, *Master Thesis* **2016**, Basel.

[230] T. Kamikubo, K. Ogasawara, *Chem. Commun.* **1996**, 1679-1680; C. K. Jana, J. Hoecker, T. M. Woods, H. J. Jessen, M. Neuburger, K. Gademann, *Angew. Chem. Int. Ed.* **2011**, *50*, 8407-8411.

[231] G. Toribio, G. Marjanet, R. Alibes, P. de March, J. Font, P. Bayon, M. Figueredo, *Eur. J. Org. Chem.* **2011**, 1534-1543; M. Á. Fresneda, R. Alibés, P. Bayón, M. Figueredo, *Eur. J. Org. Chem.* **2016**, *2016*, 3568-3574.

addition forming the isolated intermediate, which can subsequently undergo dehydration to give octalone 1*S*,2*S*-**4.3**. An aldol addition, epoxidation and dehydration pathway is less likely, since the electron rich C1=C2 double bond of the hypothetically formed bicyclic aldol addition product would not undergo epoxidation under the given reaction conditions. Additionally, the intermediacy of γ,δ-epoxy β-hydroxy ketone **4.5** rules out a pathway in which nucleophilic epoxidation takes place after aldol condensation in a 1,6-fashion to the dienone system. Cyclization of epoxy ketone 1*S*,2*R*-**4.4** (major diastereoisomer) provided access to the other octalone diastereoisomer 1*R*,2*R*-**4.3**.[232] The absolute configuration of both isomers of epoxy ketone **4.4** as well as octalone **4.3** could not be established by NOESY NMR spectroscopy. Therefore, we performed reductive cleavage of epoxy ketone 1*S*,2*R*-**4.4** to give β-hydroxy ketone **4.6** using the reactive species Na[PhSeB(OEt)$_3$] prepared *in situ* from (SePh)$_2$, NaBH$_4$ and AcOH in a 1:1 mixture of CH_2Cl_2 and EtOH.[233] NOESY NMR spectroscopy showed correlations of H1$_{ax}$ to H2, H3 and H15; of H2 to both H1$_{ax}$ and H1$_{eq}$; of H3 to H1$_{ax}$, H2, H14 and H15 (Scheme 4.2). Coupling constants for the proton signals at positions C1, C2, C3 and C4 ($^3J_{H1ax\text{-}H2eq}$ = 3.5 Hz; $^3J_{H1eq\text{-}H2eq}$ = 3.7 Hz; $^3J_{H2eq\text{-}H3ax}$ = 2.7 Hz; $^3J_{H3ax\text{-}H4ax}$ = 10.0 Hz) further corroborated the assignment of the absolute configuration at stereogenic center C2 of **4.6,** and hence provided substantial evidence for the configurational assignment of intermediates **4.3** and **4.4** obtained after epoxidation.



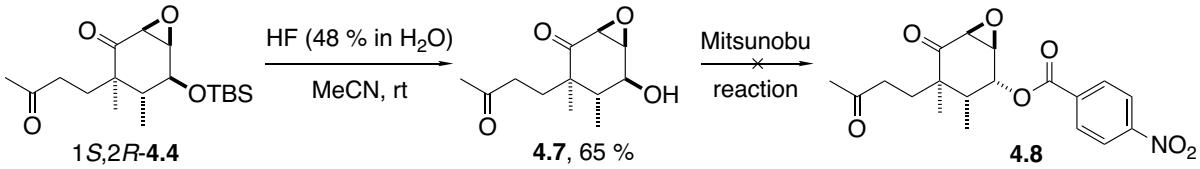
Scheme 4.2: Reductive cleavage of epoxy ketone **4.4** to β-hydroxy ketone **4.6** and key NOESY correlations for the configurational assignment of the C2 hydroxy group.

However, epoxy alcohol **4.7** was found completely unreactive towards Mitsunobu reaction conditions (up to 150°C under microwave irradiation)[234] and did not form the ester **4.8** after the TBS-protecting group in 1*S*,2*R*-**4.4** had been removed (Scheme 4.3).

[232] J. Christoffers, H. Scharl, *Eur. J. Org. Chem.* **2002**, 1505-1508.

[233] M. Miyashita, T. Suzuki, A. Yoshikoshi, *Tetrahedron Lett.* **1987**, *28*, 4293-4296; M. Miyashita, T. Suzuki, M. Hoshino, A. Yoshikoshi, *Tetrahedron* **1997**, *53*, 12469-12486.

[234] O. Mitsunobu, *Synthesis* **1981**, 1-28; K. Kim, J. K. Cha, *Angew. Chem. Int. Ed.* **2009**, *48*, 5334-5336.



Scheme 4.3: Investigation of the Mitsunobu reaction of epoxy alcohol **4.7**.

Therefore, we decided to use a route which addresses the inversion of the configuration at C3 first. TBS deprotection of enone **2.34** with aqueous HF in MeCN already set the stage for the Mitsunobu reaction. No conversion was monitored applying standard Mitsunobu protocols using PPh_3, DIAD and acetic acid as nucleophile.[234] It is well documented in literature that acetic acid can react sluggishly in the Mitsunobu reaction.[235] Therefore, we decided to investigate the reaction using the more suitable nucleophile *para*-nitrobenzoic acid. Key for the successful transformation was to use Volante's method,[236] a modified Mitsunobu procedure, which involves mixing of PPh_3 and DIAD first before adding the alcohol **4.9** and the acid to the reaction mixture at 0°C. After the mixture was warmed up to room temperature and stirred for 35 minutes, heating in the microwave at 60°C for one hour led to formation of the ester **4.10** with full inversion at C3 and 92 % yield over two steps (Scheme 4.4). Conditions used earlier for the tandem epoxidation and aldol reaction of enone **2.34** did not result in the transformation of enone **4.10** to its desired epoxy octalone. Fortunately, aldol cyclization of the ester **4.10** *via* an intermediate enamine upon reaction with pyrrolidine in the presence of AcOH furnished the doubly unsaturated octalone **4.11** in 61 % yield. There are only few literature reports on the epoxidation of γ,δ-unsaturated octalones, and unfortunately, the C1=C2 double bond could not be epoxidized by *m*-CPBA.[237] However, we succeeded to form the epoxide of monocyclic **4.10**. Epoxidation of electron-poor double bonds is usually conducted under basic conditions using a nucleophilic peroxide reagent. With the base-sensitive ester moiety at C3, a functional group necessary in the envisioned regioselective epoxide opening (**4.12** → **4.13**), we tried to find conditions avoiding hydrolysis of this ester. We were able to optimize the yield of the epoxidation reaction up to 82 % in favor of epoxy ketone **4.8** with an intact ester group on a small scale using Na_2CO_3 and H_2O_2 in an acetone/H_2O mixture.[238] However, we observed longer reaction times and decreased yields on a larger scale. After extensive screening, best

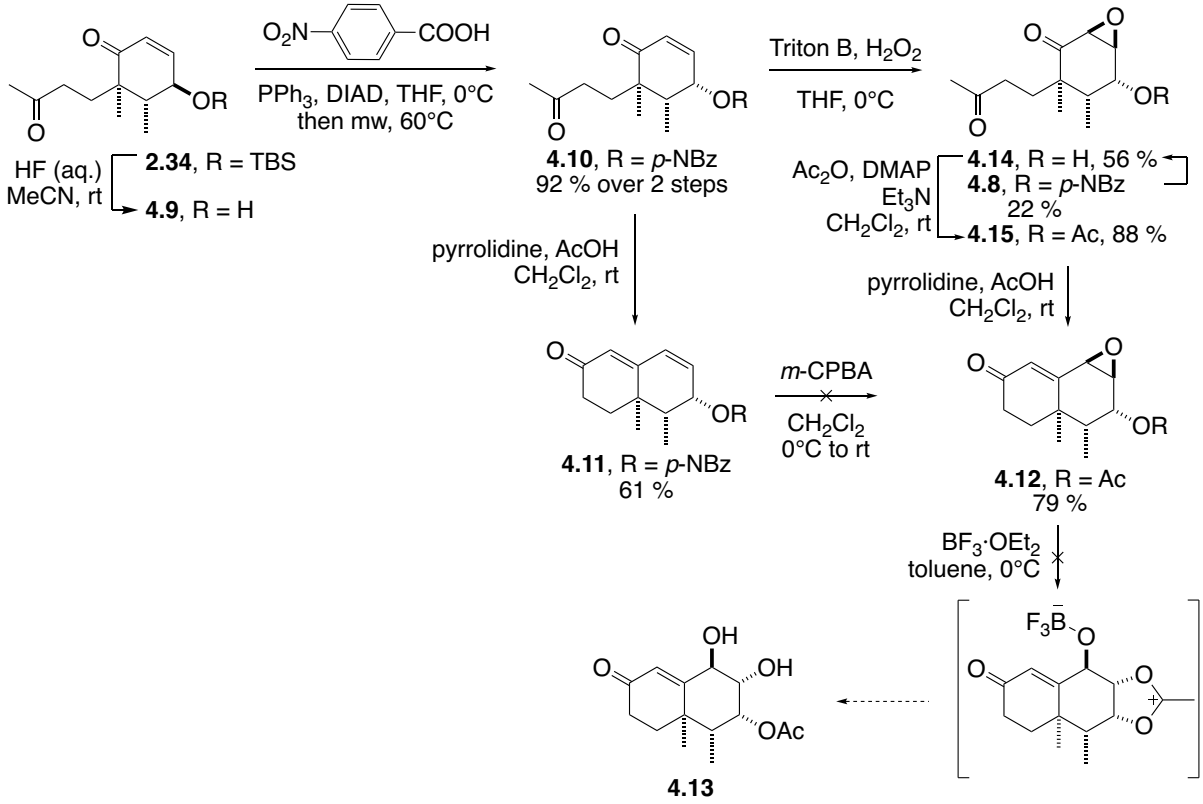
[235] D. L. Hughes, R. A. Reamer, *J. Org. Chem.* **1996**, *61*, 2967-2971.

[236] R. P. Volante, *Tetrahedron Lett.* **1981**, *22*, 3119-3122.

[237] B. W. Katona, C. L. Cummins, A. D. Ferguson, T. Li, D. R. Schmidt, D. J. Mangelsdorf, D. F. Covey, *J. Med. Chem.* **2007**, *50*, 6048-6058.

[238] S. Claessens, P. Habonimana, N. De Kimpe, *Org. Biomol. Chem.* **2010**, *8*, 3790-3795; N. R. Modugu, G. Mehta, *Tetrahedron Lett.* **2015**, *56*, 6030-6033.

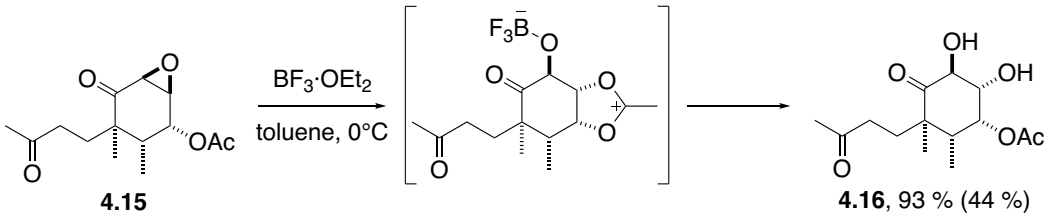
results in terms of conversion to both epoxy ketones **4.8** and **4.14** were obtained by a reagent combination of triton B and H_2O_2 in THF at 0°C, which led to formation of the two compounds in a combined yield of 78 % (**4.14**/**4.8** 5:2). The secondary hydroxy group of hydrolyzed epoxy ketone **4.14** was acetylated using standard reaction conditions (Ac_2O, Et_3N, DMAP) to give the acetoxy epoxide **4.15** in 88 % yield. With the aim to minimize the use of protecting groups, we continued by cyclizing the B-ring of epoxy ketone **4.15** and envisioned epoxide opening at a later stage. Unfortunately, neighboring group-assisted hydrolysis[231,239] on the octalone intermediate **4.12** resulted in formation of a complex mixture.



Scheme 4.4. Inversion of the hydroxy group at C3 in **4.9** by a Mitsunobu reaction, construction of the B-ring and attempted hydrolysis of the epoxide in **4.12**.

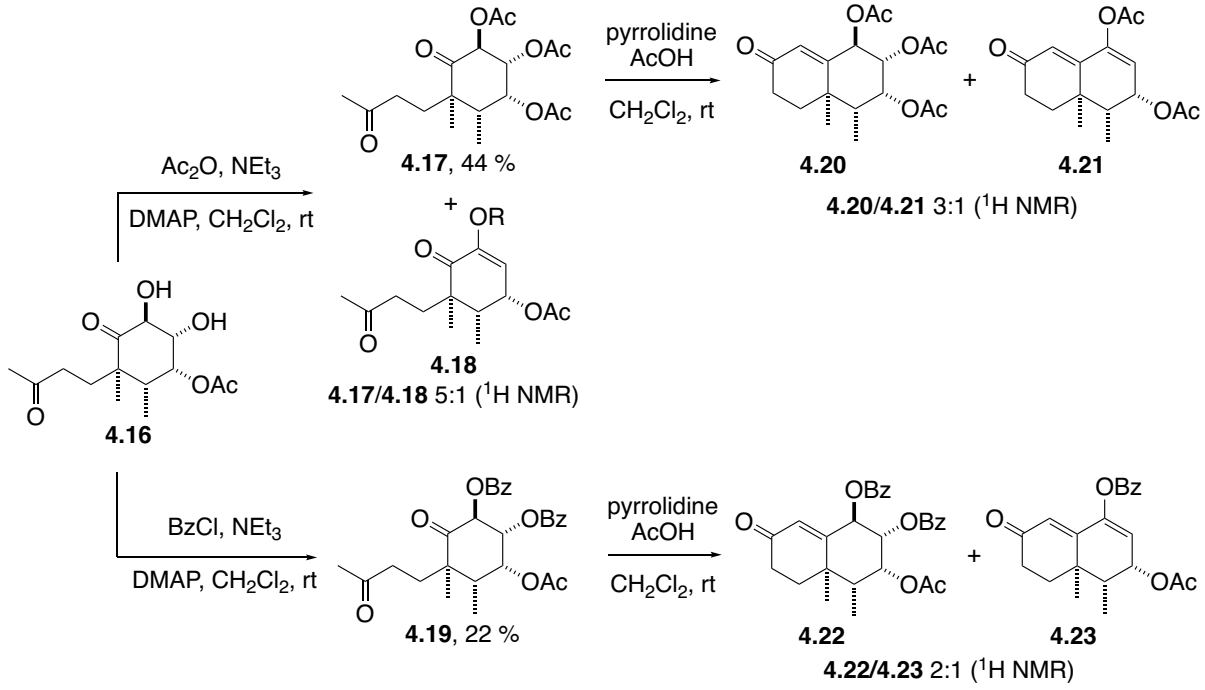
Therefore, we designed an approach with the aim to first complete the substitution pattern on the A-ring using protecting groups for the hydroxy functions at C1 and C2. Regioselective epoxide opening was triggered by treatment of **4.15** with the Lewis acid $BF_3{\cdot}OEt_2$ to form the desired triol **4.16** in 93 % yield (Scheme 4.5). Scaling up this reaction from 10 mg to >100 mg turned out to be problematic: the required reaction time was much longer (seven hours instead of two hours) and the yield dropped to 43 %.

[239] J. Aucktor, C. Anselmi, R. Brückner, M. Keller, *Synlett* **2014**, *25*, 1312-1318.



Scheme 4.5: Regioselective hydrolysis of the epoxide in **4.15**.

With **4.16** in hand, the next challenge was to find appropriate protecting groups for the *anti*-diol at C1 and C2. Ideally, these protecting groups would be cleavable under identical reaction conditions with respect to the conditions needed for cleavage of the acetyl group. Another aspect was to strive for very mild deprotection conditions as to avoid isomerization of the isopropenyl group to be installed in subsequent steps of the synthesis. Being aware that the C2 hydroxy function in β-position to the carbonyl group was prone to elimination, we initially investigated the introduction of acetyl and benzoyl protecting groups on the *anti*-diol at C1/C2. However, elimination of acetic acid or benzoic acid was observed in both the protection and the following aldol cyclization steps.

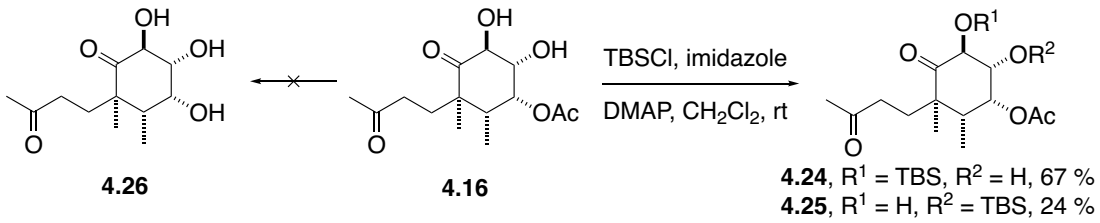


Scheme 4.6. Attempted strategies with acetyl and benzoyl protecting groups on the C1/C2 diol.

Acetylation of **4.16** using Ac_2O, Et_3N and DMAP furnished a mixture of the desired fully acetylated triol **4.17** (44 %) and elimination product **4.18** (5:1). Benzoylation of **4.16** by BzCl, Et_3N and DMAP gave only 22 % yield of the desired dibenzoylated product **4.19**. For both **4.17** and **4.19**, cyclization using pyrrolidine and AcOH resulted in partial elimination of the C2 acetyl (3:1 mixture of **4.20** and **4.21**) or C2 benzoyl (2:1 mixture of **4.22** and **4.23**) groups, respectively

(Scheme 4.6). Unsatisfactory results were also obtained for the cyclization attempts using the unprotected diol **4.16**, resulting in decomposition without formation of octalone **4.13**.

Only mono-protection at either the C1 or the C2 hydroxy group was observed in the reaction with TBSCl to form silyl ethers **4.24** and **4.25** (3:1) in a combined yield of 91 % (Scheme 4.7). Attempted removal of the acetyl group at C3 with the goal to install silicon-based protecting groups for all three hydroxy substituents only gave a complex mixture instead of unprotected triol **4.26**.



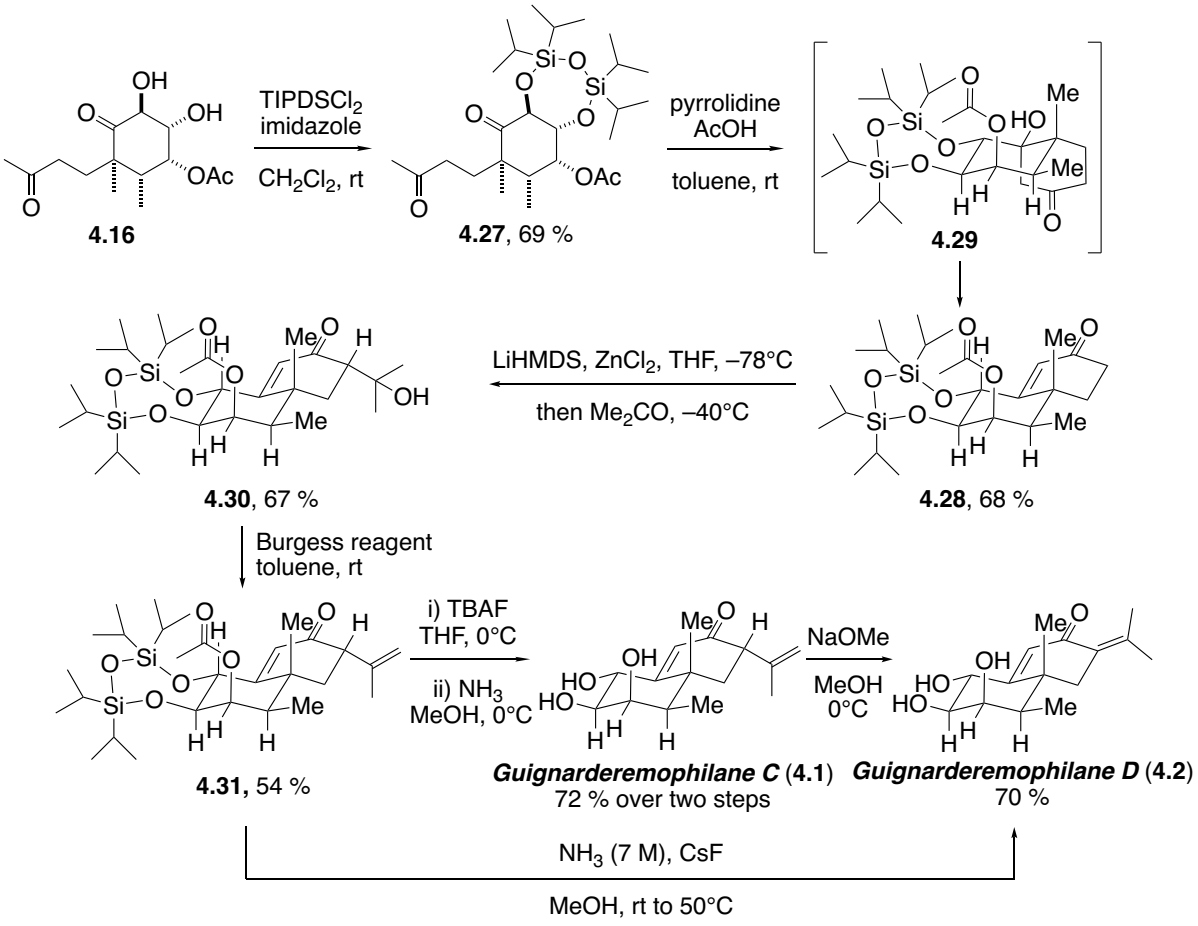
Scheme 4.7: TBS protection of C1/C2 diol and deprotection attempt for the C3–OAc group.

The reagent $TIPDSCl_2$, widely applied in carbohydrate chemistry for the protection of 1,2- and 1,3-diols,[240] was found suitable for our substrate, and the fully protected triol **4.27** was isolated in 69 % yield (Scheme 4.8). The following aldol condensation reaction with substrate **4.27** *via* an enamine intermediate generated by reaction with pyrrolidine in the presence of AcOH was successful (see Scheme 4.4), and both conversion and yield were further improved by changing the solvent from CH_2Cl_2 to the more apolar toluene to form octalone **4.28** in 68 % yield. Despite the steric demand of the TIPDS group and the imparted increase in rigidity of the A-ring due to its fusion to an additional seven-membered silyloxy ring, intramolecular aldol addition to the ketone at C10 still took place. Studying the structure of the aldol addition intermediate **4.29** (Scheme 4.8), it is discernible that the bottom face of the A-ring is not overly shielded from the TIPDS group in pseudo-equatorial orientation. Upon elimination of water, we now had octalone **4.28** in hand and addressed the installation of the isopropenyl group for targeting the sesquiterpene skeleton. Similar procedures on octalones using a two-step procedure have already been described in literature:[241] first, aldol addition to acetone gives the

[240] M. Lalonde, T. H. Chan, *Synthesis* **1985**, 817-845; A. G. Myers, P. M. Harrington, E. Y. Kuo, *J. Am. Chem. Soc.* **1991**, *113*, 694-695.

[241] S. Torii, T. Inokuchi, K. Kawai, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 861-866; T. Kitahara, H. Kurata, K. Mori; M. C. Witschel, H. J. Bestmann, *Tetrahedron Lett.* **1995**, *36*, 3325-3328; R. Riclea, J. S. Dickschat, *Angew. Chem. Int. Ed.* **2015**, *54*, 12167-12170.

tertiary alcohol, which is then dehydrated regioselectively using Burgess reagent.[242] For the aldol step, we had to slightly modify the literature procedure and add the acetone to the enolate at –40°C, as previous experiments had shown no conversion and full recovery of starting material when the electrophile was added at –78°C. In case of our substrate, the seven-membered ring of the TIPDS group influences the conformation of the A- and B-ring and might thus lower the reactivity of the enolate formed by deprotonation of **4.28**. Upon modification of the known procedure, we isolated the desired tertiary alcohol **4.30** in an acceptable yield of 67 % with full diastereoselectivity.



Scheme 4.8. Construction of the B-ring and endgame in the synthesis of guignarderemophilanes C (**4.1**) and D (**4.2**).

To complete the installation of the three-carbon side chain, regioselective elimination of water from **4.30** was achieved by treatment with Burgess reagent to give the isopropenylated octalone **4.31** as the desired elimination product in a modest yield of 54 %. Using triflic

[242] G. M. Atkins, E. M. Burgess, *J. Am. Chem. Soc.* **1968**, *90*, 4744-4745; P. Crabbe, C. Leon, *J. Org. Chem.* **1970**, *35*, 2594-2596; D. B. Ushakov, V. Navickas, M. Ströbele, C. Maichle-Mössmer, F. Sasse, M. E. Maier, *Org. Lett.* **2011**, *13*, 2090-2093.

anhydride and DIPEA[241c] instead of the milder Burgess reagent resulted in the formation of a complex mixture. Having all substituents installed, the endgame of the synthesis was addressed by deprotection of both the TIPDS and acetyl groups. With a combination of CsF and ammonia in methanol at 50°C,[243] all protecting groups were cleaved. However, formation of guignarderemophilane C (**4.1**) was not observed, as the alkaline reaction conditions turned out to effect isomerization of the C=C double bond of the isopropenyl group to provide guignarderemophilane D (**4.2**) instead. Therefore, in order to avoid isomerization and to give access to **4.1**, a milder two-step procedure was developed. Compound **4.31** was treated with TBAF as fluoride anion source to cleave the TIPDS group and after work-up, the acetyl group was removed by reaction with ammonia in methanol at room temperature.

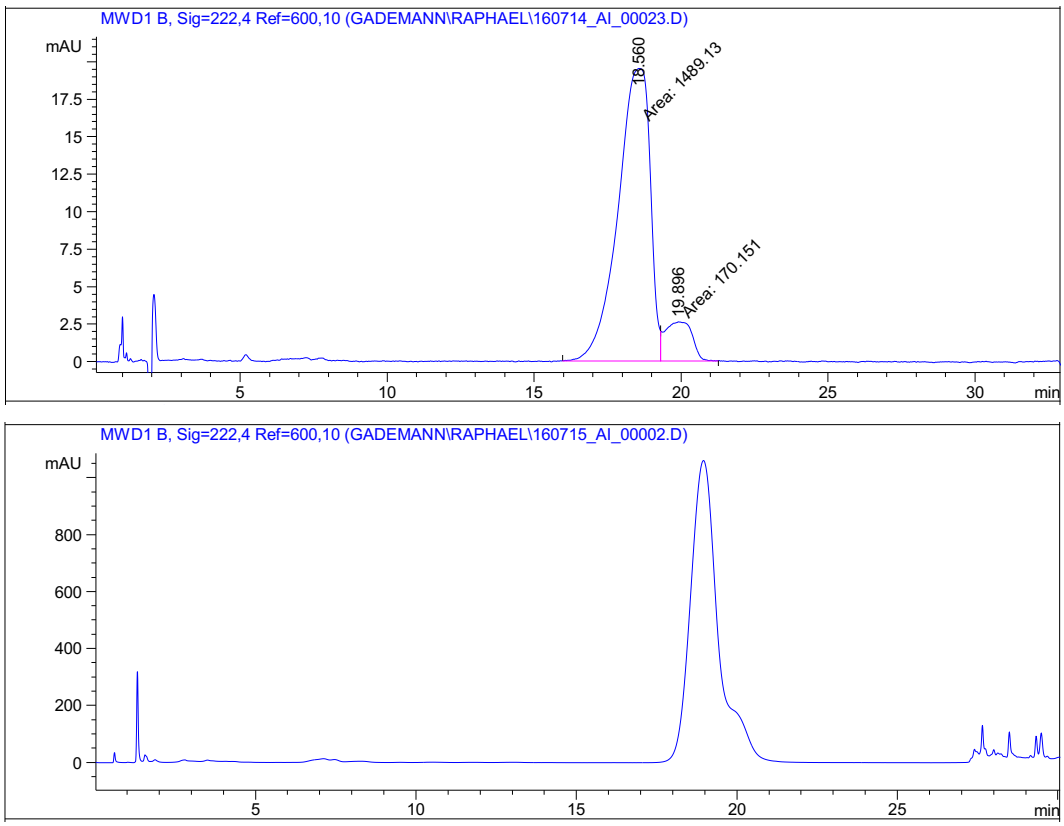


Figure 4.3: Analytical (top, column: Synergi Hydro-RP 4 µm 80 Å, 150 mm x 4.6 mm; solvent A: H_2O; solvent B: MeCN; flow = 1.0 mL/min; T = rt; UV detection at λ = 222 nm; solvent system: isocratic, [B] = 18 %) and preparative RP-HPLC chromatograms of guignarderemophilanes C and D (bottom, column: Synergi Hydro-RP 10 µm 80 Å, 150 mm x 10.0 mm; solvent A: H_2O; solvent B: MeCN; flow = 4.6 mL/min; T = rt; UV detection at λ = 222 nm; solvent system: isocratic, [B] = 18 %.).

[243] J. R. McCarthy, D. P. Matthews, D. M. Stemerick, E. W. Huber, P. Bey, B. J. Lippert, R. D. Snyder, P. S. Sunkara, *J. Am. Chem. Soc.* **1991**, *113*, 7439-7440.

Both natural products were obtained after evaporation of the solvent and the ratio of the two natural product isomers slightly increased to 4.6:1 (**4.1**/**4.2**) in favor of **4.2** upon purification by flash column chromatography. A reasonable separation of the isomers was accomplished by reversed-phase HPLC resulting in pure guignarderemophilane C (**4.1**) and guignarderemophilane D (**4.2**, Figure 4.3). Optimized separation conditions on the analytical HPLC column Synergi Hydro-RP 4 µm 80 Å (150 mm x 4.6 mm) by an isocratic eluent of 18 % MeCN in water (flow = 1.0 mL/min, R_t = 18.6 min for **4.1** and 19.9 min for **4.2**) were successfully reproduced on the semi-preparative column Synergi Hydro-RP 10 µm 80 Å (150 mm x 10.0 mm, flow = 4.5 mL/min, R_t = 18.0 min for **4.1** and 19.2 min for **4.2**). Alternatively, guignarderemophilane D (**4.2**) was obtained from its isomer **4.1** by treatment with NaOMe in MeOH at 0°C in 70 % yield.

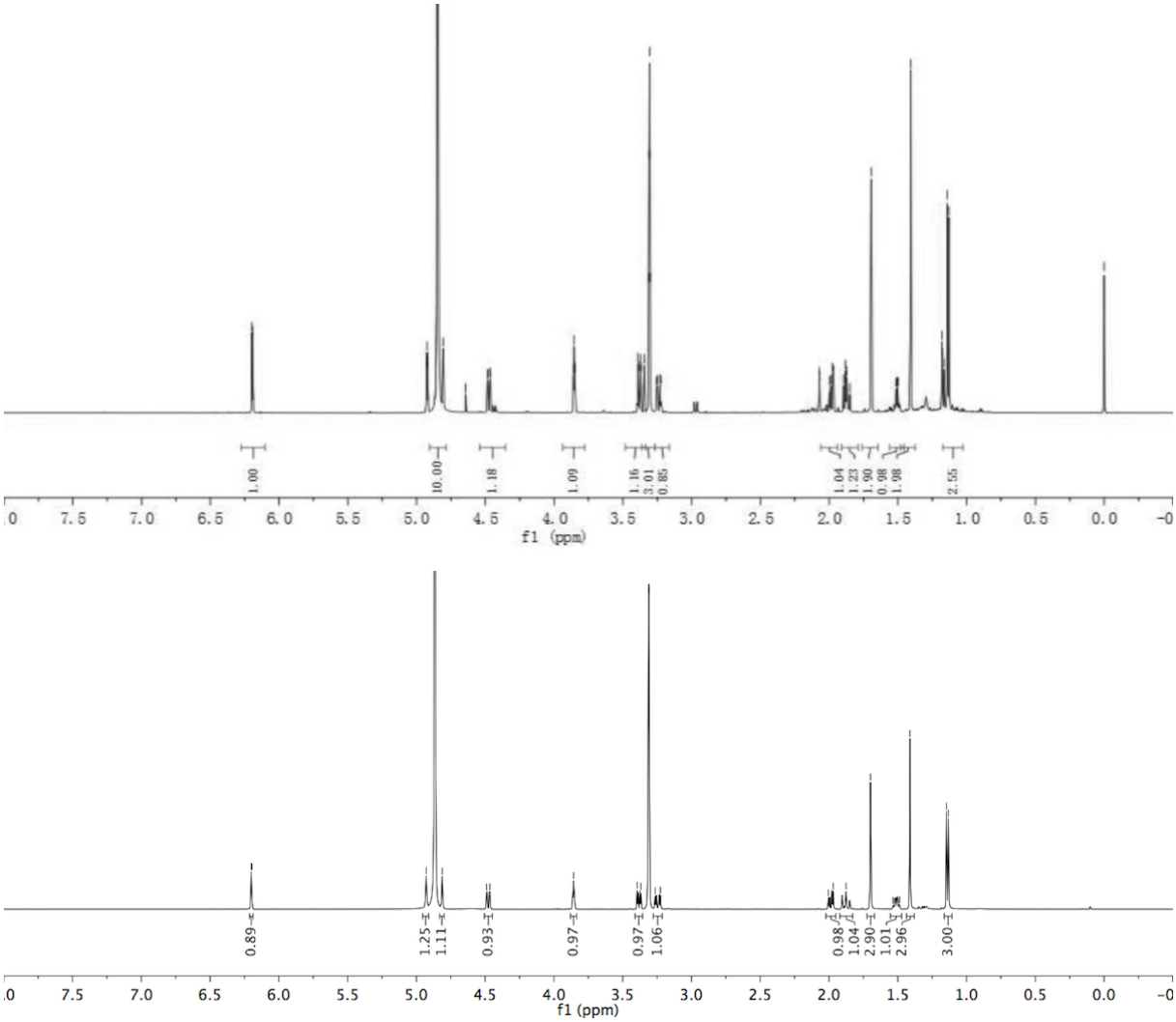
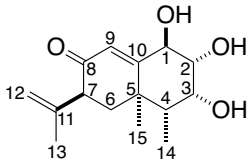


Figure 4.4: ^{1}H NMR spectra (in MeOD-d_4) of natural (top) and synthetic (bottom) guignarderemophilane C (**4.1**).[227]

The NMR spectra (^{1}H and ^{13}C) of both the synthetic compounds were in agreement with those reported for the isolated natural products (Table 4.1 and Table 4.2),[9] but for the optical rotation values we observed substantial differences and opposite signs for both compounds: our measured optical rotation value for guignarderemophilane C was $[\alpha]_D^{27} = +35°$ (c = 0.88, MeOH) and the reported value $[\alpha]_D^{20} = -175°$ (c = 0.01, MeOH). The values for guignarderemophilane D were $[\alpha]_D^{27} = +38°$ (c = 0.70, MeOH) for the synthetic and $[\alpha]_D^{20} = -121°$ (c = 0.12, MeOH) for the isolated material, as reported in literature. In order to provide evidence for the identity of the isolated natural products and the synthetic material, we measured a CD spectrum of synthesized **4.1**, which was in agreement with the one reported in literature (Figure 4.5).

Table 4.1: ^{1}H and ^{13}C NMR data of natural and synthetic guignarderemophilane C (**4.1**).



position	natural 4.1 δ_H lit.[a, b] (600 MHz, MeOD-d_4)	synthetic 4.1 δ_H this work[b] (500 MHz, MeOD-d_4)	natural 4.1 δ_C lit.[a] (150 MHz, MeOD-d_4)	synthetic 4.1 δ_C this work (126 MHz, MeOD-d_4)
1	4.47 (dd, 10.2, 1.8)	4.48 (dd, 10.4, 2.0)	70.1	70.1
2	3.39 (dd, 10.2, 3.0)	3.38 (dd, 10.4, 3.3)	77.4	77.4
3	3.85 (t, 3.0)	3.86 (t, 3.0)	75.6	75.6
4	1.50 (m)	1.51 (qd, 7.1, 2.8)	45.8	45.8
5			40.8	40.8
6	1.99 (dd, 12.0, 4.8)	1.99 (dd, 13.0, 4.6)	44.3	44.4
	1.88 (dd, 12.0, 9.0)	1.88 (t, 13.7)		
7	3.23 (dd, 15.0, 4.8)	3.24 (dd, 14.4, 4.6)	51.3	51.3
8			201.8	201.7
9	6.19 (d, 1.8)	6.20 (d, 2.0)	122.0	122.0
10			172.6	172.6
11			144.9	144.9
12	4.93 (t, 1.8)	4.93 (t, 1.7)	114.7	114.7
	4.81 (brs)	4.80–4.82 (m)		
13	1.69 (s)	1.70 (t, 1.0)	20.2	20.2
14	1.13 (d, 6.6)	1.14 (d, 7.1)	11.8	11.8
15	1.41 (s)	1.41 (s)	19.7	19.7

[a] See reference 227 for published NMR spectroscopic data of natural **4.1**. [b] coupling constants $J_{H\text{-}H}$ are given in parentheses (Hz).

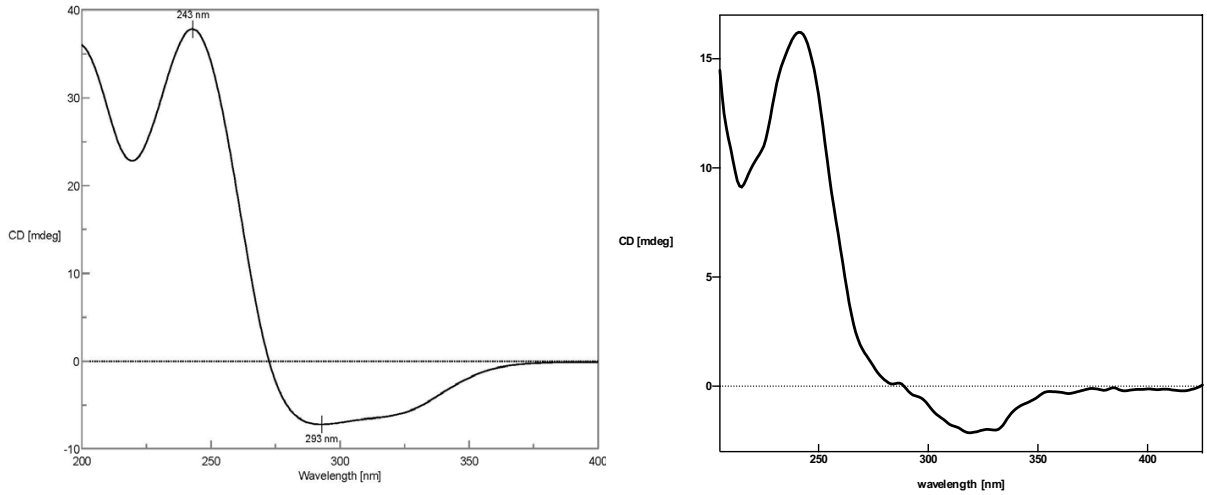


Figure 4.5: Reported CD spectrum of isolated guignarderemophilane C (**4.1**) in MeOH (left)[227] and CD spectrum of synthetic **4.1** in MeOH (c = 0.2 mM, right).

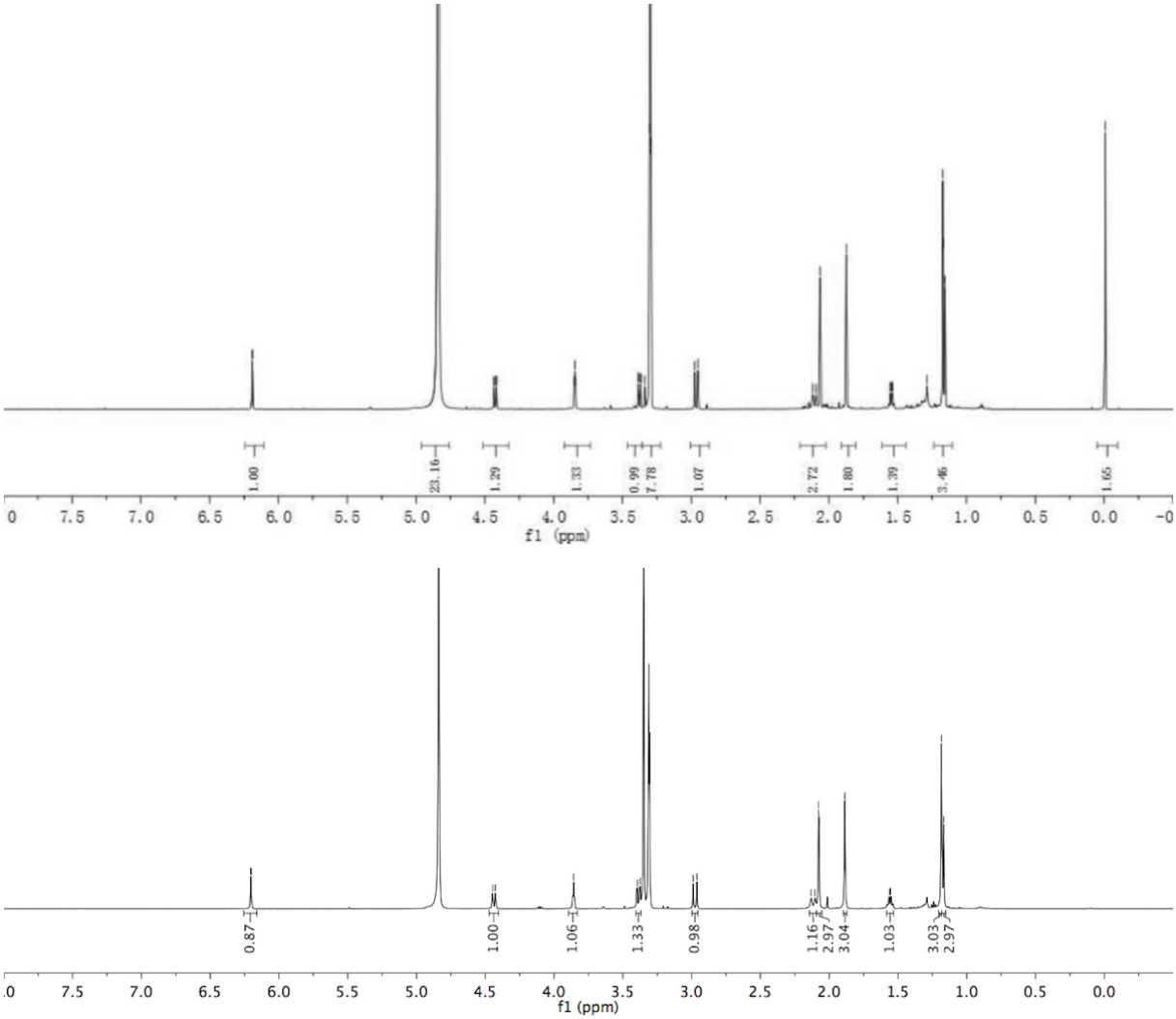
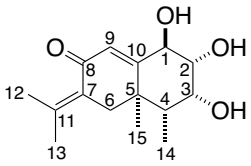


Figure 4.6: ^{1}H NMR spectra (in MeOD-d_4) of natural (top) and synthetic (bottom) guignarderemophilane D (**4.2**).[227]

Table 4.2: ^{1}H and ^{13}C NMR data of natural and synthesized guignarderemophilane D (**4.2**).



position	natural 4.2 δ_H lit.[a, b] (600 MHz, MeOD-d_4)	synthetic 4.2 δ_H this work[b] (500 MHz, MeOD-d_4)	natural 4.2 δ_C lit.[a] (150 MHz, MeOD-d_4)	synthetic 4.2 δ_C this work (126 MHz, MeOD-d_4)
1	4.43 (dd, 10.3, 1.8)	4.43 (dd, 10.4, 2.2)	70.1	70.1
2	3.39 (dd, 10.2, 3.6)	3.38 (dd, 10.3, 3.3)	77.6	77.6
3	3.85 (t, 3.0)	3.86 (t, 2.9)	75.6	75.6
4	1.56 (m)	1.55 (qd, 7.1, 2.7)	44.7	44.8
5			43.0	43.1
6	2.97 (d, 13.8)	2.98 (d, 13.6)	43.6	43.7
	2.11 (d, 13.8)	2.12 (d, 14.3)		
7			145.6	145.5
8			194.2	194.2
9	6.19 (s)	6.19 (d, 2.2)	124.2	124.2
10			171.2	171.3
11			128.6	128.7
12	2.07 (s)	2.08 (d, 2.1)	22.8	22.8
13	1.88 (s)	1.89 (d, 1.4)	22.4	22.4
14	1.16 (d, 6.0)	1.18 (d, 1.4)	12.1	12.1
15	1.18 (s)	1.17 (s)	20.1	20.1

[a] See reference 227 for published NMR spectroscopic data of natural **4.2**. [b] coupling constants $J_{H\text{-}H}$ are given in parentheses (Hz).

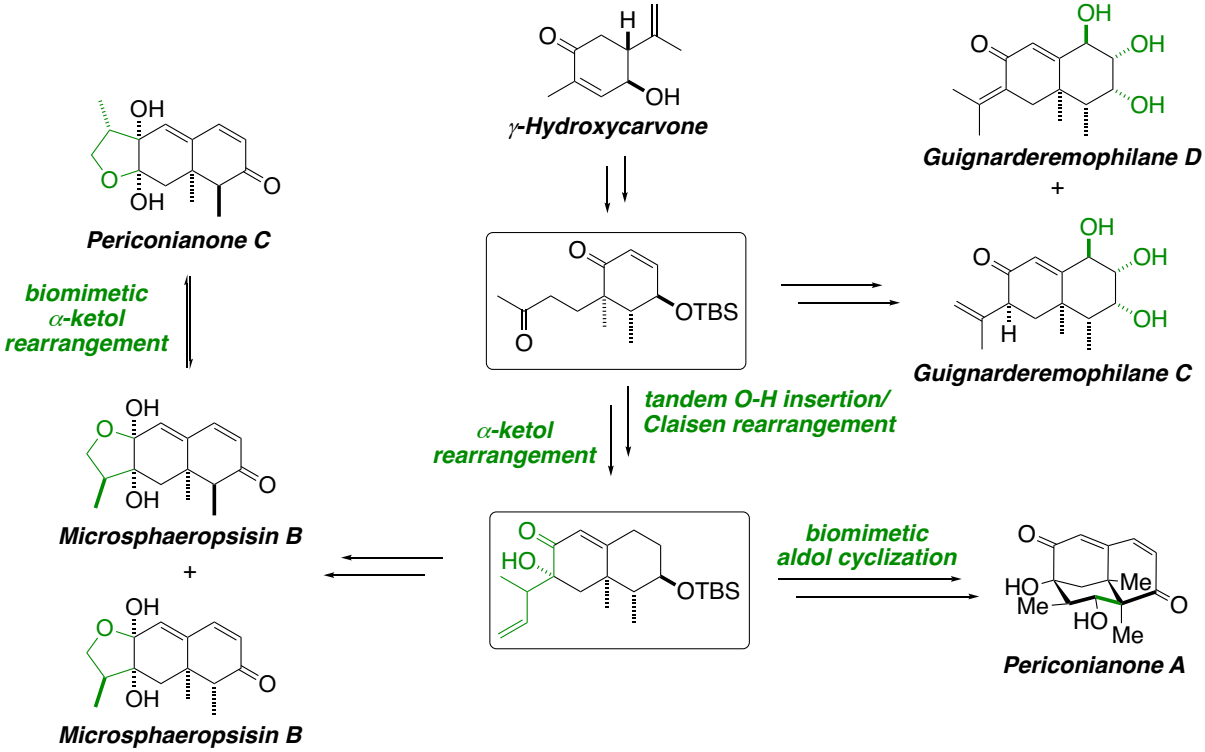
4.3 Conclusion

In conclusion, we present the first total syntheses of the polyoxygenated eremophilane-type sesquiterpenes guignarderemophilane C (**4.1**) and D (**4.2**) by applying a concise route with the intermediacy of enone **2.34**. Starting from γ-hydroxy carvone (**2.40**), both syntheses have been achieved in 15 and 14 steps, respectively. Installation of the three hydroxy groups in the A-ring was identified as a key challenge, which was successfully tackled by applying a Mitsunobu inversion, epoxidation and regioselective hydrolysis of the epoxide with neighboring-group participation. The synthesis was successfully accomplished by establishing all stereogenic centers in the A-ring before the B-ring was constructed by aldol cyclization. Additionally, in the course of our synthetic endeavor, we observed a spontaneous aldol condensation under specific epoxidation reaction conditions. In order to find more potent neural anti-inflammatory active agents, derivatization of both the natural products and synthetic intermediates is envisioned.

5 CONCLUSION

The present PhD thesis encompasses synthetic and biogenetic studies on eremophilane sesquiterpenoids, which culminated in the successful total syntheses of periconianone A and C, microsphaeropsisin B and C as well as guignarderemophilane C and D by a divergent approach.

Synthetic investigations on periconianone A are presented in **Chapter 2**. Starting from known γ-hydroxy carvone, the total synthesis of this complex tricarbocyclic sesquiterpenoid was achieved in 15 linear steps. Key transformations on the way to periconianone A are a Criegee fragmentation, a Rh-mediated O–H insertion followed by spontaneous Claisen reaction and α-ketol rearrangement, and a biomimetic late-stage aldol cyclization to construct the tricarbocyclic framework.



The discovery that bicyclic α-allylated α-hydroxyketones in the eremophilane skeleton can undergo 1,2-shifts led to the biogenetic hypothesis presented in **Chapter 3**. Based on the structural similarities of microsphaeropsisin B and periconianone C, both isolated from endophytic fungi, a novel proposal on the biosynthesis of C8–C11-connected furanoeremophilanes was elaborated. To provide evidence by organic synthesis, an enantioselective synthesis of microsphaeropsisin B and C starting from the α-allylated α-hydroxyketone intermediate in the periconianone A synthesis was investigated first. Having successfully synthesized microsphaeropsisin B and C, suitable reaction conditions for the rearrangement of these two natural products into their regioisomers periconianone C and 4-*epi*-

periconianone C were devised. The obtained findings provide strong experimental evidence for the biogenetic hypothesis of microsphaeropsisin B being a biosynthetic precursor of periconianone C, and hint at the occurrence of other eremophilane-type terpenoids bearing a C8–C11 linkage.

Finally, in **Chapter 4** the total syntheses of the polyoxygenated eremophilane-type sesquiterpenes guignarderemophilane C and D starting from a diketone intermediate of the periconianone A synthesis are presented. The main challenge in this synthetic endeavor was the installation of the three contiguous hydroxy groups in the A-ring, which was finally met by a route comprising a Mitsunobu inversion, epoxidation and regioselective epoxide opening. With specific epoxidation conditions, we observed spontaneous aldol condensation, which directly led to formation of the octalone core. Altogether, key to the successful synthesis of guignarderemophilane C and D was the installation of all stereogenic centers on the A-ring before the B-ring was closed by an intramolecular aldol addition.

6 EXPERIMENTAL PART

6.1 General Methods and Materials

All chemicals have been purchased from Acros, Alfa Aesar, Fluorochem or Sigma-Aldrich and were used without further purification (except for Et_3N, which was freshly distilled before use). All reactions have been carried out in flame-dried glassware (unless aqueous reagents were used) and reactions involving air sensitive compounds have been performed under an argon or nitrogen atmosphere. Solvents applied for chemical transformations were either anhydrous quality or HPLC grade solvents, which have been dried by filtration through activated aluminum oxide under nitrogen (H_2O content <10 ppm, Karl-Fischer titration). For work-up and purification, solvents have been distilled from technical grade. All synthetic transformations have been monitored by either thin layer chromatography (TLC) or ^1H NMR spectroscopy. Yields refer to purified, dried and spectroscopically pure compounds. TLC was performed on Merck silica gel 60 F254 plates (0.25 mm thickness) pre-coated with a fluorescent indicator. Concentration under reduced pressure was performed by rotary evaporation at 40°C or by lyophilization. Flash chromatography was performed using silica gel 60 (230-400 mesh) from SiliCycle or Sigma-Aldrich with a forced flow eluent at 0.1–0.3 bar pressure. HPLC was performed by using an Agilent 1100 series instrument equipped with reversed-phase columns for analytical separation or semi-preparative separation; or by using a modular Shimadzu HPLC instrument (CBM-20A system controller, SPD-20A UV/Vis detector, LC-20A solvent delivery unit, SIL-20A auto-sampler, CTO-20A column oven, and DGU-20A online degassing unit) equipped with reversed-phase columns for analytical separation, semi-preparative separation or preparative separation. All ^1H and ^{13}C NMR spectra were recorded using a Bruker 250 MHz, 400 MHz or 500 MHz (^1H) & 63 MHz, 101 MHz or 126 MHz (^{13}C) spectrometer at room temperature (unless otherwise stated). Chemical shifts (δ-values) are reported in ppm, spectra were calibrated relative to the residual proton chemical shifts ($CHCl_3$, δ = 7.26; DMSO-d_5, δ = 2.50; MeOD-d_3, δ = 3.31) and carbon chemical shifts ($CDCl_3$, δ = 77.16; DMSO-d_6, δ = 39.52; MeOD-d_4, δ = 49.00) of the solvents; multiplicity is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and coupling constant *J* is given in Hz. IR spectra were recorded on a Varian 800 FT-IR ATR Spectrophotometer or a Perkin Elmer SpectrumTwo ATR-FTIR. The absorptions are reported in cm^{-1}. All HRMS-ESI mass spectra were recorded by the Mass Spectrometric Service of the University of Basel on a QTOF-ESI spectrometer (Bruker maXis 4G) or the Mass Spectrometric Service of the University of Zurich on a QExactive instrument (Thermo Fisher Scientific, Bremen, Germany) equipped with a

heated electrospray (ESI) ionization source and connected to a Dionex Ultimate 3000 UHPLC system. HRMS-EI mass spectra were measured by the Mass Spectrometric Service of the University of Zurich on a Thermo DFS (ThermoFisher Scientific, Bremen, Germany) double-focusing magnetic sector mass spectrometer (geometry BE): mass spectra were measured in electron impact (EI) mode at 70 eV, with solid probe inlet, source temperature of 200°C, acceleration voltage of 5 kV, and resolution of 2'500. Melting points (M.p.) were determined using a Büchi B-545 apparatus in open capillaries and are uncorrected. Optical rotations $°[\alpha]_D^T$ were measured at the sodium D line using a 1 mL cell with 1 dm path length, or a 0.2 mL cell with 0.1 dm path length on a Jasco P-2000 digital polarimeter and the concentration c is given in g/100 mL $CHCl_3$ or MeOH. CD spectra were acquired on a JASCO J-810 spectrometer. X-ray analyses performed at the University of Basel: Data collections for both crystal structures were performed at low temperature (123 K) using Mo K_a radiation on a *Bruker KappaAPEX diffractometer*. Integration of the frames and data reduction was carried out using APEX2.[244] The structures were solved by direct methods using SIR92.[245] All non-hydrogen atoms were refined using anisotropically by full-matrix least squares on *F* using CRYSTALS.[246] Hydrogen atoms were placed in calculated positions by means of the "riding" model. X-ray analyses performed at the University of Zurich: The single crystal X-ray measurements at the University of Zurich were made on a Rigaku Oxford Diffraction SuperNova area-detector diffractometer using Cu K_a radiation ($\lambda = 1.54184$ Å) from a micro-focus X-ray source and an Oxford Instruments Cryojet XL cooler.

6.2 Abbreviations, Acronyms and Symbols

°C ..... degree centigrade
Å ..... ångström
Ac ..... acetyl
AIBN ..... azobisisobutyronitrile
aq. ..... aqueous
atm ..... atmosphere
BINOL ..... 1,1'-bi-2-naphthol
Bn ..... benzyl
Bu ..... butyl

[244] Bruker Analytical X-ray Systems Inc., **2006**, *Apex2*, Version 2 User Manual, M86-E01078,Madison, WI.

[245] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Cryst.* **1994**, *27*, 435-436.

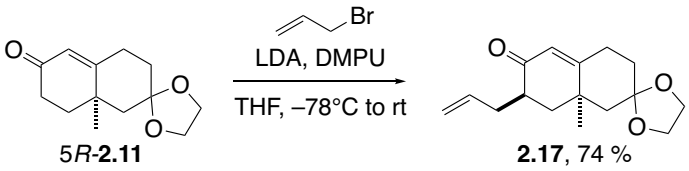
[246] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Cryst.* **2003**, *36*, 1487.

Bz ..... benzoyl
cat. ..... catalyst
cm ..... centimeter
CD ..... circular dichroism
CPBA ..... chloroperoxybenzoic acid
Cy ..... cyclohexyl
δ ..... NMR chemical shift
d ..... doublet
d ..... deci
DBU ..... 1,8-diazabicyclo(5.4.0)undec-7-ene
DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHF ..... dihydrofuran
DHP ..... dihydropyran
DIAD ..... diisopropyl azodicarboxylate
DIBAL ..... diisobutylaluminium
DIPEA ..... *N*,*N*'-diisopropylethylamine
DMAP 4-dimethylaminopyridine
DMAPP ..... dimethylallyl diphosphate
DMF ..... dimethylformamide
DMP ..... Dess-Martin periodinane
DMPU ..... *N*,*N*'-dimethylpropyleneurea
DMSO ..... dimethyl sulfoxide
dr ..... diastereomeric ratio
ECD ..... electronic circular dichroism
ee ..... enantiomeric excess
EI ..... electron ionization
ESI ..... electrospray ionization
Et ..... ethyl
equiv. ..... equivalent
FPP ..... farnesyl pyrophosphate
FT ..... Fourier transform
g ..... gram
h ..... hour
HMDS ..... hexamethyldisilazan
HMPA ..... hexamethylphosphoramide

HPLC ..... high-performance liquid chromatography
HRMS ..... high-resolution mass spectrometry
Hz ..... hertz
IBX ..... 2-iodoxybenzoic acid
IPP ..... isopentenyl diphosphate
IR ..... infrared
J ..... NMR coupling constant
L ..... ligand
L ..... liter
LDA ..... lithium diisopropylamide
LTMP ..... lithium tetramethylpiperidide
µ ..... micro
m ..... multiplet
m ..... milli
m ..... meter
M ..... molar, mol L^{-1}
M ..... mega
M.p. ..... melting point
Me ..... methyl
min ..... minute
MOM ..... methoxymethyl
MPO ..... *p*-methoxypyridine *N*-oxide
Ms ..... mesyl
MS ..... mass spectrometry
MS ..... molecular sieve
MVK ..... methyl vinyl ketone
mw ..... microwave
n ..... nano
NBS ..... *N*-bromosuccinimide
NMR ..... nuclear magnetic resonance spectroscopy
NOESY ..... nuclear Overhauser effect spectroscopy
o.n. ..... overnight
ORD ..... optical rotatory dispersion
QTOF ..... quadrupole time-of-flight
PCC ..... pyridinium chlorochromate

PDC ..... pyridinium dichromate
Ph..... phenyl
PMB.....*p*-methoxybenzyl
ppm..... parts per million
PPTS..... pyridinium *p*-toluenesulfonate
Pr .....propyl
q..... quartet
R_f..... retention factor
RP .....reversed phase
R_t..... retention time
rt ..... room temperature
s ..... singlet
S.....solvent
SAR .....structure–activity relationship
sat. .....saturated
SEM..... 2-(trimethylsilyl)ethoxymethyl
SM .....starting material
t.....triplet
TBA ..... tetrabutylammonium
TBD ..... 1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBHP .....*tert*-butyl hydroperoxide
TBS.....*tert*-butyldimethylsilyl
TES.....triethylsilyl
Tf..... triflic
TFA .....trifluoroacetic acid
THF .....tetrahydrofuran
THP ..... tetrahydropyran
TIPDS.....tetraisopropyldisiloxane
TLC .....thin layer chromatography
TMS..... trimethylsilyl
Ts..... tosyl
UHPLC ..... ultra high-performance liquid chromatography
UV .....ultraviolet
$\tilde{\nu}$.....wavenumber
WMK.....Wieland-Miescher ketone

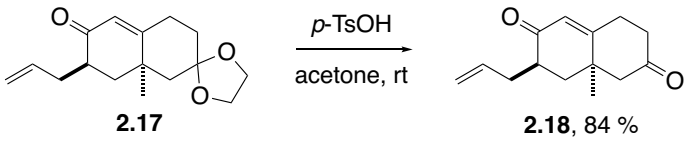
6.3 Total Synthesis of Periconianone A



5*R*-**2.11** **2.17**, 74 %

(7*R*,8a*R*)-7-Allyl-8a-methyl-1,3,4,7,8,8a-hexahydro-6*H*-spiro[naphthalene-2,2'-[1,3]dioxolan]-6-one (2.17): To a cooled (–78°C) solution of diisopropylamine (102 µL, 0.720 mmol, 1.6 equiv.) in THF (3.0 mL) was added *n*-BuLi (1.6 M in THF, 422 µL, 0.675 mmol, 1.5 equiv.) dropwise *via* syringe. The resulting solution was stirred for 40 min at this temperature, before a solution of 5*R*-**2.11** (100 mg, 0.450 mmol, 1.0 equiv.) in THF (0.5 mL) was added. The mixture was stirred at –78°C for 30 min and then DMPU (61 µL, 0.495 mmol, 1.1 equiv.) and allyl bromide (0.16 mL, 1.80 mmol, 4.0 equiv.) were added dropwise. After stirring at –78°C was continued for 20 min, the mixture was allowed to warm up to rt o.n. The mixture was quenched by addition of sat. aq. NH_4Cl solution and diluted with H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 3:1) to give **2.17** (87 mg, 0.332 mmol, 74 %) as a white slurry.

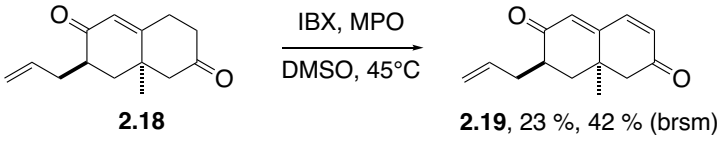
TLC: R_f = 0.6 (SiO_2, pentane/Et_2O 1:1). **FTIR** (neat): $\tilde{\nu}$ = 2920, 2360, 1709, 1666, 1434, 1362, 1291, 1238, 1187, 1106, 1066, 1030, 1008, 916, 878 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.83 – 5.71 (m, 1H), 5.76 (d, *J* = 1.2, 1H), 5.05 (d, *J* = 10.7, 1H), 5.05 – 4.98 (m, 1H), 4.06 – 3.97 (m, 2H), 3.96 – 3.87 (m, 2H), 2.76 – 2.69 (m, 1H), 2.66 (ddd, *J* = 14.7, 5.0, 1.8, 1H), 2.48 (ddt, *J* = 13.0, 8.5, 4.3, 1H), 2.30 (ddd, *J* = 14.8, 4.6, 2.6, 1H), 2.07 (dt, *J* = 15.4, 8.0, 1H), 1.91 (ddt, *J* = 13.1, 5.3, 2.8, 1H), 1.84 (dd, *J* = 12.8, 4.2, 1H), 1.80 (dd, *J* = 12.7, 2.1, 1H), 1.70 – 1.61 (m, 1H), 1.61 – 1.51 (m, 2H), 1.38 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 200.3, 167.3, 136.4, 124.5, 116.8, 108.1, 64.9, 63.9, 48.2, 44.4, 41.4, 37.3, 35.2, 33.6, 30.3, 23.6. **HRMS** (ESI) Exact mass calculated for $C_{16}H_{23}O_3^+$ $[M+H]^+$: 263.1642, found: 263.1639; for $C_{16}H_{22}NaO_3^+$ $[M+Na]^+$: 285.1461, found: 285.1458.



2.17 **2.18**, 84 %

(7*R*,8a*R*)-7-Allyl-8a-methyl-1,3,4,7,8,8a-hexahydronaphthalene-2,6-dione (2.18): To a solution of **2.17** (250 mg, 0.953 mmol, 1.0 equiv.) in acetone (10.0 mL) was added *p*-TsOH (181 mg, 0.953 mmol, 1.0 equiv.) and the solution was stirred at rt for 4 h. The mixture was diluted with H_2O and Et_2O, and the layers were separated. The aqueous layer was extracted with Et_2O (2 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 3:2) to give **2.18** (174 mg, 0.797 mmol, 84 %) as a colorless solid.

TLC: R_f = 0.50 (SiO_2, pentane/Et_2O 1:2); 0.32 (SiO_2, pentane/Et_2O 1:1). **FTIR** (neat): $\tilde{\nu}$ = 2966, 2917, 2865, 1707, 1664, 1434, 1360, 1290, 1253, 1188, 1081, 1029, 1006, 953, 915, 880, 771 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.91 (s, 1H), 5.82 – 5.70 (m, 1H), 5.10 – 5.05 (m, 1H), 5.05 – 5.02 (m, 1H), 2.86 – 2.75 (m, 1H), 2.75 – 2.67 (m, 2H), 2.56 – 2.50 (m, 2H), 2.50 – 2.43 (m, 1H), 2.38 (s, 2H), 2.12 (dtd, *J* = 14.4, 8.0, 1.2, 1H), 1.91 (dd, *J* = 13.4, 4.7, 1H), 1.72 (t, *J* = 13.7, 1H), 1.26 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 208.3, 199.5, 163.3, 135.9, 125.6, 117.3, 54.6, 43.3, 41.6, 40.1, 40.0, 33.5, 31.4, 24.0. **HRMS** (ESI) Exact mass calculated for $C_{14}H_{19}O_2^+$ $[M+H]^+$: 219.1380, found: 219.1378; for $C_{14}H_{18}NaO_2^+$ $[M+Na]^+$: 241.1199, found: 241.1196.

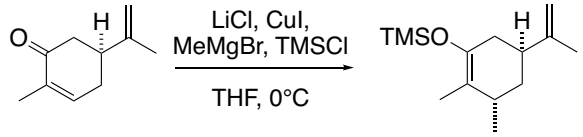


2.18 **2.19**, 23 %, 42 % (brsm)

(7*R*,8a*R*)-7-Allyl-8a-methyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (2.19): IBX (405 mg, 1.37 mmol, 3.0 equiv.) and MPO·H_2O (172 mg, 1.37 mmol, 3.0 equiv.) were dissolved in DMSO (2.5 mL) under stirring for 30 min at 45°C. The mixture was then charged with **2.18** (100 mg, 0.458 mmol, 1.0 equiv.) and stirring was continued for 2 d at 45°C. The turbid reaction mixture was quenched by addition of sat. aq. $NaHCO_3$ solution and diluted with H_2O. The obtained solution was extracted with Et_2O (3 x) and the combined organic layers were washed with sat. aq. $NaHCO_3$ solution and H_2O, dried over Na_2SO_4, filtered and evaporated to give a 1:1 mixture of desired product **2.19** and SM **2.18** (^{1}H NMR, total 65 mg crude). The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to give **2.19**

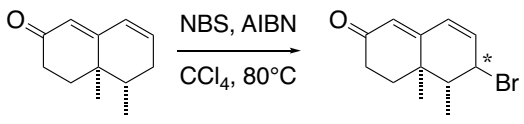
(22.6 mg, 0.104 mmol, 23 %) as a yellow oil and recovered SM **2.18** (18.6 mg, 85 µmol, 19 %) as colorless needles.

TLC: R_f = 0.65 (SiO_2, pentane/Et_2O 1:2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.04 (d, *J* = 9.9, 1H), 6.18 (d, *J* = 9.8, 1H), 6.05 (s, 1H), 5.81 – 5.68 (m, 1H), 5.11 – 5.06 (m, 1H), 5.06 – 5.03 (m, 1H), 2.77 – 2.69 (m, 1H), 2.57 (ddt, *J* = 13.0, 8.6, 4.4, 1H), 2.47 (s, 2H), 2.18 (dtt, *J* = 14.3, 7.9, 1.1, 1H), 1.95 (dd, *J* = 13.3, 4.8, 1H), 1.78 (t, *J* = 13.6, 1H), 1.32 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 199.8, 197.9, 157.1, 143.2, 135.6, 132.0, 129.1, 117.5, 51.7, 42.1, 41.8, 37.1, 33.7, 24.6. **HRMS** (ESI) Exact mass calculated for $C_{14}H_{16}NaO_2^+$ $[M+Na]^+$: 239.1043, found: 239.1039.



S-(+)-Carvone **2.24**, 68 %, *dr* > 10:1

(((3*S*,5*S*)-2,3-Dimethyl-5-(prop-1-en-2-yl)cyclohex-1-en-1-yl)oxy)trimethylsilane (2.24): LiCl (28 mg, 0.67 mmol, 0.2 equiv.) was flame-dried *in vacuo*. CuI (63 mg, 0.33 mmol, 0.1 equiv.) and dry THF (10 mL) were added. The mixture was stirred until a clear green solution was formed and then cooled to 0°C. *S*-Carvone (500 mg, 3.33 mmol, 1.0 equiv.) and TMSCl (0.47 mL, 3.66 mmol, 1.1 equiv.) were added sequentially to form a yellow solution. After 10 min, a solution of MeMgBr (3 M in Et_2O, 1.33 mL, 4.00 mmol, 1.2 equiv.) was added dropwise and the formed suspension was stirred for 30 min at 0°C. The reaction mixture was quenched by addition of sat. aq. NH_4Cl solution and extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane, 1 % Et_3N) to give **2.24** (537 mg, 2.25 mmol, 68 %, *dr* >10:1) as a colorless oil. Analytical data of **2.24** is in accordance to reference 75.

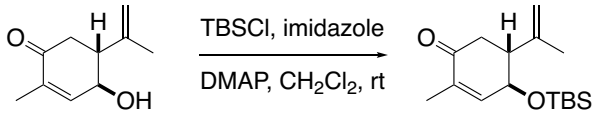


2.23 **2.31**, 51 %, *dr* 1:1

(4a*R*,5*R*,6*R*)-6-Bromo-4a,5-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one (3*R*-2.31) and (4a*R*,5*R*,6*S*)-6-bromo-4a,5-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one (3*S*-2.31): A solution of diene dione **2.23** (50 mg, 0.284 mmol, 1.0 equiv.), NBS (76 mg,

0.426 mmol, 1.5 equiv.) and AIBN (4.7 mg, 0.028 mmol, 0.1 equiv.) in CCl_4 (3.0 mL) was heated at 80°C for 18 h. The mixture was allowed to cool to rt, before pentane was added to precipitate the succinimide. The obtained suspension was filtered through a short pad of Celite and the filtrate was concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to give brominated octalone **2.31** (36.8 mg, 0.284 mmol, 51 %, *dr* 1:1) as a yellow oil.

TLC: $\boldsymbol{R_f}$ = 0.59 and 0.63 (SiO_2, pentane/Et_2O 1:2). **^{1}H NMR** (400 MHz, $CDCl_3$, signals are marked with [a] or [b] corresponding to their diastereoisomers) δ = 6.36[a] (dd, *J* = 9.6, 5.0, 1H), 6.35 – 6.31[b] (m, 1H), 6.24[a] (dd, *J* = 9.7, 0.8, 1H), 6.12[b] (dd, *J* = 9.8, 2.0, 1H), 5.79[b] (s, 1H), 5.78[a] (s, 1H), 4.88[a] (t, *J* = 4.9, 1H), 4.62[b] (dt, *J* = 10.1, 2.2, 1H), 2.65[b] (dd, *J* = 14.4, 5.5, 1H), 2.60[a] (dd, *J* = 14.4, 5.5, 1H), 2.55 – 2.42[a+b] (m, 2H), 2.14 – 1.98[a+b] (m, 2H), 1.91 – 1.64[a+b] (m, 4H), 1.29[a] (s, 3H), 1.22[b] (d, *J* = 6.8, 3H), 1.22[a] (d, *J* = 6.8, 3H), 1.10[b] (s, 3H).

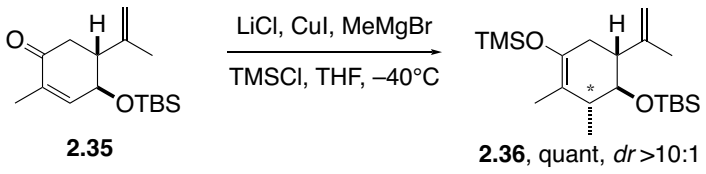


2.40 **2.35**, 66 %

(4*S*,5*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one (2.35): To a solution of 4*S*,5*R*-4-hydroxy carvone (**2.40**, 5.54 g, 33.3 mmol, 1.0 equiv.), imidazole (6.80 g, 99.9 mmol, 3.0 equiv.) and DMAP (1.02 g, 8.33 mmol, 0.25 equiv.) in dry CH_2Cl_2 (140 mL) was added TBSCl (10.0 g, 66.6 mmol, 2.0 equiv.), and the reaction mixture was stirred for 3 h at rt. The reaction was quenched with sat. aq. NH_4Cl solution and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 10:1) to give **2.35** (6.12 g, 21.9 mmol, 66 %) as a yellowish oil.

TLC: $\boldsymbol{R_f}$ = 0.60 (SiO_2, pentane/Et_2O 6:1). **Optical rotation**: $[\alpha]_D^{24}$ = +148.6° (c = 0.56, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2955, 2930, 2893, 2858, 2362, 2340, 1682, 1470, 1362, 1254, 1083, 865, 837, 776 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.53 (dq, *J* = 2.8, 1.5 Hz, 1H), 4.89 (p, *J* = 1.6 Hz,1H), 4.87 – 4.83 (m, 1H), 4.40 (dp, *J* = 9.1, 2.0 Hz, 1H), 2.72 (ddd, *J* = 13.2, 9.1, 4.5 Hz, 1H), 2.48 (dd, *J* = 16.2, 4.5 Hz, 1H), 2.40 (dd, *J* = 16.2, 12.8 Hz, 1H), 1.78 (dd, *J* = 1.7 Hz, 3H), 1.73 (dd, *J* = 1.5, 0.8 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 199.2, 148.9, 143.8, 134.8, 114.0, 70.5, 52.5, 41.4, 25.9 (3C), 20.5, 18.2,

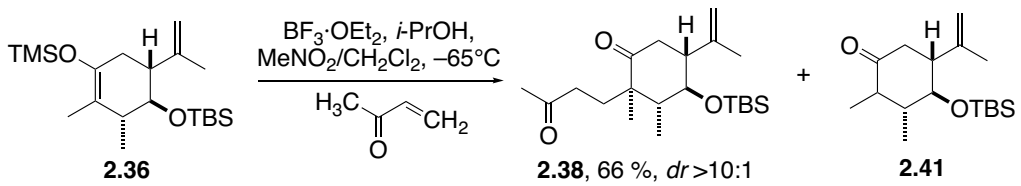
15.6, -4.2, -4.6. **HRMS** (ESI) Exact mass calculated for $C_{16}H_{28}NaO_2Si^+$ $[M+Na]^+$: 303.1745, found: 303.1751.



2.35 **2.36**, quant, *dr* >10:1

***tert*-Butyl(((1*S*,2*R*,6*R*)-2,3-dimethyl-6-(prop-1-en-2-yl)-4-((trimethylsilyl)oxy)cyclohex-3-en-1-yl)oxy)dimethylsilane (2.36):** LiCl (185 mg, 4.36 mmol, 0.2 equiv.) was flame-dried *in vacuo*. CuI (415 mg, 2.18 mmol, 0.1 equiv.) and dry THF (135 mL) were added. The mixture was stirred until a clear green solution was formed and then cooled to –40°C. **2.35** (6.12 g, 21.8 mmol, 1.0 equiv.) in dry THF (30 mL) and TMSCl (3.04 mL, 24.0 mmol, 1.1 equiv.) were added sequentially to form a yellow solution. After 10 min, a solution of MeMgBr (3 M in Et_2O, 8.72 mL, 26.2 mmol, 1.2 equiv.) was added dropwise and the formed suspension was stirred for 30 min at –40°C. The reaction mixture was then quenched by addition of sat. aq. NH_4Cl solution and extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give **2.36** (8.0 g, 21.7 mmol, quant., *dr* >10:1) as a yellow oil.

TLC: R_f = 0.99 (SiO_2, pentane/Et_2O 6:1), 0.80 (Al_2O_3, pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.82 – 4.78 (m, 2H), 3.46 (dd, *J* = 9.5, 6.6 Hz, 1H), 2.40 (td, *J* = 9.8, 5.4 Hz, 1H), 2.20 – 2.11 (m, 1H), 2.11 – 1.98 (m, 2H), 1.72 (t, *J* = 1.1 Hz, 3H), 1.53 – 1.51 (m, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.16 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 146.4, 141.6, 113.9, 112.6, 77.6, 49.2, 43.5, 34.6, 26.2 (3C), 21.2, 18.6, 18.2, 14.0, 0.8 (3C), -3.2, -3.6.

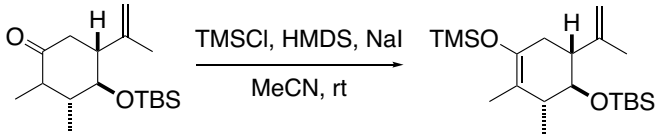


2.36 **2.38**, 66 %, *dr* >10:1 **2.41**

(2*R*,3*R*,4*S*,5*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-2,3-dimethyl-2-(3-oxobutyl)-5-(prop-1-en-2-yl)cyclohexan-1-one (2.38): A solution of **2.36** (16.6 g, 45.0 mmol, 1.0 equiv.) in dry CH_2Cl_2 (210 mL) was cooled to –78°C. $MeNO_2$ (7.3 mL, 3.0 equiv.), *i*-PrOH (10.3 mL, 3.0 equiv.) and MVK (7.3 mL, 90.0 mmol, 2.0 equiv.) were added sequentially. After stirring the reaction

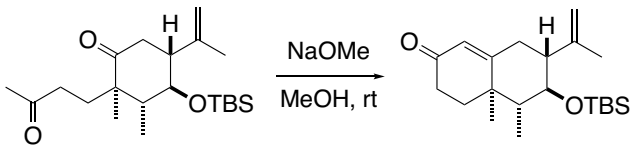
mixture for 5 min, $BF_3 \cdot Et_2O$ (6.84 mL, 54.0 mmol, 1.2 equiv.) was added dropwise and the mixture was allowed to warm to –65°C. After 3.5 h at this temperature, additional $BF_3 \cdot Et_2O$ (0.57 mL, 0.1 equiv.) was added, stirred o.n. and the reaction mixture was then quenched by addition of sat. aq. $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3 x) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 3:1) to give **2.38** (10.9 g, 29.8 mmol, 66 %, *dr* >10:1) as a colorless solid. Desilylated starting material **2.41** (4.26 g, 14.35 mmol, 32 %) was obtained as a yellow oil.

M.p. = 77.7 – 79.8°C. TLC: $\boldsymbol{R_f}$ = 0.38 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{24}$ = +22.8° (c = 0.63, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2957, 2932, 2893, 2857, 2362, 2340, 1712, 1649, 1463, 1435, 1363, 1255, 1164, 1075, 886, 836, 775, 680 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 4.85 – 4.82 (m, 2H), 3.75 (t, *J* = 9.2 Hz, 1H), 2.59 (dd, *J* = 14.3, 12.8 Hz, 1H), 2.49 – 2.39 (m, 2H), 2.34 – 2.25 (m, 2H), 2.14 (s, 3H), 1.95 (ddd, *J* = 14.3, 11.2, 4.6 Hz, 1H), 1.76 – 1.69 (m, 1H), 1.71 (dd, *J* = 1.5, 0.9 Hz, 3H), 1.65 – 1.58 (m, 1H), 1.05 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 213.8, 208.9, 144.6, 114.3, 73.9, 52.8, 50.3, 44.5, 41.6, 38.8, 30.1, 29.4, 26.3 (3C), 20.5, 20.3, 18.5, 12.7, -3.0, -3.4. **HRMS** (ESI) Exact mass calculated for $C_{21}H_{38}NaO_3Si^+$ $[M+Na]^+$: 389.2482, found: 389.2483.



2.41 **2.36**, 84 %

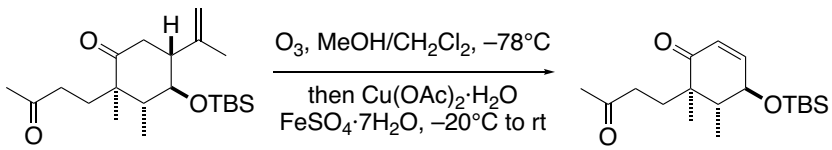
***tert*-Butyl(((1*S*,2*R*,6*R*)-2,3-dimethyl-6-(prop-1-en-2-yl)-4-((trimethylsilyl)oxy)cyclohex-3-en-1-yl)oxy)dimethylsilane (2.36):** Ketone **2.41** (9.04 g, 30.5 mmol, 1.0 equiv.) in MeCN (200 mL) was added to a solution of NaI (18.3 g, 122 mmol, 4.0 equiv.), TMSCl (11.7 mL, 91.5 mmol, 3.0 equiv.) and HMDS (25.9 mL, 122 mmol, 4.0 equiv.) in MeCN (20 mL) at rt. The mixture was stirred for 2 h before it was quenched by addition of sat. aq. NH_4Cl solution (pH < 7) and extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was filtered through a short plug of silica (pentane/Et_2O 20:1) to give **2.36** (9.43 g, 25.6 mmol, 84 %) as a colorless oil.



2.38 **2.42**, 84 %

(4a*R*,5*R*,6*S*,7*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-4a,5-dimethyl-7-(prop-1-en-2-yl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.42): To a solution of **2.38** (300 mg, 0.818 mmol, 1.0 equiv.) in MeOH (3.0 mL) was added a solution of NaOMe (0.5 M in MeOH, 1.96 mL, 0.982 mmol, 1.2 equiv.) and the mixture was stirred for 20 h at rt to form an orange solution. H_2O was added and the mixture was extracted with Et_2O (3 x). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 4:1) to give **2.42** (238 mg, 0.683 mmol, 84 %) as a yellowish oil.

M.p. = 79.9 – 80.8°C. TLC: R_f = 0.50 (SiO_2, pentane/Et_2O 2:1). **Optical rotation**: $[\alpha]_D^{25}$ = +49.0° (c = 0.90, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2930, 2896, 2855, 1671, 1469, 1429, 1360, 1251, 1188, 1120, 1075, 1020, 953, 888, 834, 774, 707, 672 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.75 (d, *J* = 1.5 Hz, 1H), 4.85 (q, *J* = 1.2 Hz, 2H), 3.56 (t, *J* = 9.7 Hz, 1H), 2.52 – 2.44 (m, 1H), 2.40 (ddd, *J* = 16.9, 13.8, 4.9 Hz, 1H), 2.34 (dddd, *J* = 16.9, 5.3, 3.4 Hz, 0.9 Hz, 1H), 2.25 – 2.16 (m, 2H), 2.04 (ddd, *J* = 13.5, 5.0, 3.4 Hz, 1H), 1.73 (t, *J* = 1.1 Hz, 3H), 1.76 – 1.69 (m, 1H), 1.45 – 1.37 (m, 1H), 1.14 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 199.5, 169.1, 145.5, 124.1, 114.0, 74.4, 54.1, 50.3, 39.4, 37.4, 36.1, 33.6, 26.4 (3C), 20.8, 18.6, 17.6, 12.0, -2.8, -3.3. **HRMS** (ESI) Exact mass calculated for $C_{21}H_{36}NaO_2Si^+$ $[M+Na]^+$: 371.2377, found: 371.2381.

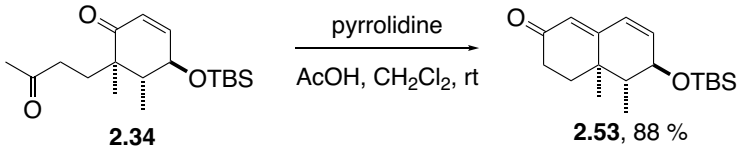


2.38 **2.34**, 67 %

(4*R*,5*R*,6*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-5,6-dimethyl-6-(3-oxobutyl)cyclohex-2-en-1-one (2.34): A solution of **2.38** (250 mg, 0.686 mmol, 1.0 equiv.) and Sudan III (spatula tip) in CH_2Cl_2/MeOH (6.0 mL, 1:2) was cooled to –78°C and O_3 was bubbled through the solution until the red color disappeared. The solution was purged with N_2 for 5 min and the mixture was warmed to –20°C. $Cu(OAc)_2 \cdot H_2O$ (272 mg, 1.36 mmol, 2.0 equiv.) was added, followed by $FeSO_4 \cdot 7H_2O$ (228 mg, 0.818 mmol, 1.2 equiv.) after 30 min. The mixture was stirred for 1 h

and then allowed to slowly warm to rt o.n. Aq. HCl solution (0.1 M) was added and the mixture was stirred for 30 min before the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 3:1) to give **2.34** (148 mg, 0.456 mmol, 67 %) as a colorless solid.

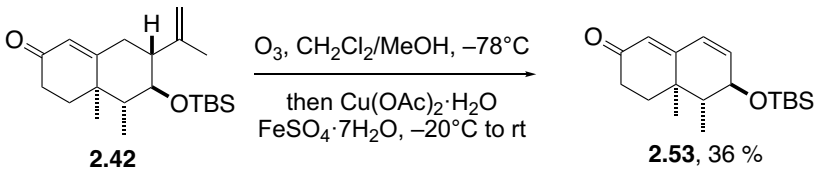
M.p. = 79.9 – 83.8°C. TLC: R_f = 0.62 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = –102.7° (c = 0.51, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2933, 2897, 2857, 1716, 1668, 1463, 1413, 1367, 1293, 1250, 1200, 1168, 1070, 1006, 940, 873, 841, 778, 719, 691, 659 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.70 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.86 (dd, *J* = 10.3, 2.1 Hz, 1H), 4.18 (dt, *J* = 9.1, 2.0 Hz, 1H), 2.37 – 2.20 (m, 2H), 2.21 – 2.07 (m, 1H), 2.12 (s, 3H), 2.04 – 1.93 (m, 1H), 1.65 – 1.56 (m, 1H), 1.01 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 208.6, 203.3, 151.5, 127.4, 71.2, 48.5, 42.9, 38.5, 30.0, 28.7, 25.9 (3C), 19.4, 18.2, 11.3, -4.1, -4.6. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{33}O_3Si^+$ $[M+H]^+$: 325.2193, found: 325.2193; for $C_{18}H_{32}NaO_3Si^+$ $[M+Na]^+$: 347.2013, found: 347.2014.



2.34 **2.53**, 88 %

(4a*R*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-4a,5-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one (2.53): A mixture of **2.34** (20.0 mg, 62 µmol, 1.0 equiv.), pyrrolidine (6.1 µL, 74 µmol, 1.2 equiv.) and AcOH (4.2 µL, 74 µmol, 1.2 equiv.) in CH_2Cl_2 (1.0 mL) was stirred for 22 h at rt. After 22 h aq. HCl (1.0 M) and Et_2O were added and the layers were separated. The aqueous layer was extracted with Et_2O (2 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 3:1) to give **2.53** (16.6 mg, 54 µmol, 88 %) as colorless crystals.

or

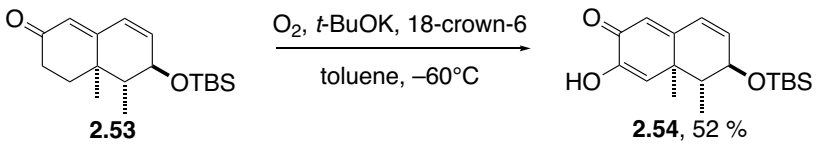


2.42 **2.53**, 36 %

A solution of **2.42** (50 mg, 0.143 mmol, 1.0 equiv.) and Sudan III (spatula tip) in CH_2Cl_2/MeOH (3.0 mL, 5:1) was cooled to –78°C and O_3 was bubbled through the solution

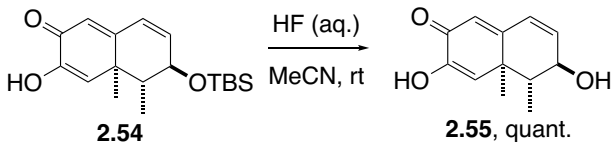
until the red color disappeared. The mixture was purged with O_2 and Ar and allowed to warm up to –20°C. $Cu(OAc)_2 \cdot H_2O$ (57.1 mg, 0.286 mmol, 2.0 equiv.) was added, followed by $FeSO_4 \cdot 7H_2O$ (47.7 mg, 0.172 mmol, 1.2 equiv.) after 20 min. The suspension was stirred at –20°C for 3 h, then slowly warmed up to rt and stirred o.n. H_2O was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x) and the combined organic layers were washed with sat. aq. $NaHCO_3$ solution, brine and H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 3:1) to give **2.53** (15.8 mg, 0.052 mmol, 36 %) as colorless solid.

M.p. = 46.5 – 47.4°C. TLC: $\boldsymbol{R_f}$ = 0.50 (SiO_2, pentane/Et_2O 2:1). **Optical rotation**: $[\alpha]_D^{24}$ = +35.5° (c = 0.39, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2953, 2857, 2361, 1668, 1464, 1353, 1257, 1131, 1080, 1022, 943, 878, 836, 776, 668 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.10 (dd, *J* = 10.0, 1.6 Hz, 1H), 6.06 (dd, *J* = 10.0, 1.5 Hz, 1H), 5.73 (s, 1H), 4.08 (d, *J* = 9.4 Hz, 1H), 2.54 (ddd, *J* = 17.9, 14.5, 5.3 Hz, 1H), 2.41 (dddd, *J* = 17.9, 5.2, 2.2, 1.0 Hz, 1H), 2.03 (ddd, *J* = 13.2, 5.4, 2.3 Hz, 1H), 1.75 (td, *J* = 13.9, 5.2 Hz, 1H), 1.61 (dq, *J* = 9.4, 6.8 Hz, 1H), 1.09 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 199.5, 162.4, 141.2, 127.8, 124.5, 71.8, 47.3, 37.4, 34.0, 33.4, 26.0 (3C), 18.2, 16.4, 10.7, -3.9, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{31}O_2Si^+$ $[M+H]^+$: 307.2088, found: 307.2083; for $C_{18}H_{30}NaO_2Si^+$ $[M+Na]^+$: 329.1907, found: 329.1902.



(4a*S*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-4a,5-dimethyl-5,6-dihydronaphthalen-2(4a*H*)-one (2.54): To a solution of **2.53** (16.6 mg, 54 µmol, 1.0 equiv.) and 18-crown-6 (21.5 mg, 81 µmol, 1.5 equiv.) in toluene (1.0 mL) at –60°C (dry-ice/acetone bath) was added *t*-BuOK (15.2 mg, 0.135 mmol, 2.5 equiv.). O_2 was bubbled through the reaction mixture for 2 min and the orange solution was allowed to stir under an O_2 atmosphere (1 atm) for further 30 min. After TLC showed full consumption of the starting materials, the mixture was quenched by addition of aq. HCl solution (0.1 M, pH = 5) and extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 3:1) to give diosphenol **2.54** (9.0 mg, 28 µmol, 52 %) as a colorless solid.

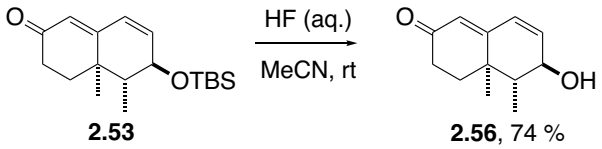
M.p. = 91.2 – 95.4°C. TLC: R_f = 0.66 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = –88.2° (c = 0.45, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ =3383, 2955, 2931, 2857, 1642, 1258, 1228, 1197, 1062, 892, 867, 837, 776 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.40 (s, 1H), 6.33 (dd, *J* = 10.0, 1.8, 1H), 6.33 (s, 1H), 6.22 (d, *J* = 0.7, 1H), 6.08 (dd, *J* = 10.0, 2.3, 1H), 4.07 – 3.99 (m, 1H), 1.65 (dq, *J* = 9.1, 6.7, 1H), 1.22 (d, *J* = 6.8, 3H), 1.11 (s, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.13 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 181.2, 164.6, 146.9, 139.6, 127.4, 121.9, 121.6, 71.8, 46.1, 43.3, 25.9 (3C), 21.6, 18.1, 12.0, -3.8, -4.4. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{28}NaO_3Si^+$ $[M+Na]^+$: 343.1700, found: 343.1701.



2.54 **2.55**, quant.

(4a*S*,5*R*,6*R*)-3,6-Dihydroxy-4a,5-dimethyl-5,6-dihydronaphthalen-2(4a*H*)-one (2.55): To a solution of **2.54** (7.0 mg, 22 μmol, 1.0 equiv.) in MeCN (0.5 mL) was added a solution of HF (48 % in H_2O, 9 µL, 0.218 mmol, 10.0 equiv.). The mixture was stirred for 3 h and then quenched by addition of sat. aq. $NaHCO_3$ solution. The mixture was extracted with Et_2O (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 1:2) to give **2.55** (4.5 mg, 22 µmol, quant.) as a yellowish solid.

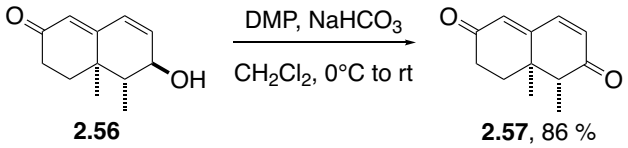
M.p. = 114.5 – 115.9°C. TLC: R_f = 0.57 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{24}$ = –13.6° (c = 0.37, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3366, 2976, 1619, 1426, 1304, 1218, 1029, 892 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.41 (s, 1H), 6.39 (dd, *J* = 10.0, 2.2, 1H), 6.33 (s, 1H), 6.24 (d, *J* = 0.7, 1H), 6.20 (dd, *J* = 9.9, 2.3, 1H), 4.03 (d, *J* = 9.3, 1H), 1.61 (brs, 1H), 1.57 – 1.53 (m, 1H), 1.31 (d, *J* = 6.7, 3H), 1.12 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 181.2, 164.2, 147.0, 138.6, 128.2, 122.0, 121.7, 71.3, 46.5, 43.2, 21.5, 11.8. **HRMS** (ESI) Exact mass calculated for $C_{12}H_{14}NaO_3^+$ $[M+Na]^+$: 229.0835, found: 229.0836.



2.53 **2.56**, 74 %

(4a*R*,5*R*,6*R*)-6-Hydroxy-4a,5-dimethyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one (2.56): To a solution of **2.53** (78.1 mg, 0.255 mmol, 1.0 equiv.) in MeCN (3.0 mL) was added a solution of HF (48 % in H_2O, 54 µL, 1.28 mmol, 5.0 equiv.) at rt. The mixture was stirred for 5 h and then quenched by addition of sat. aq. $NaHCO_3$ solution. The mixture was extracted with Et_2O (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 1:1 to 100 % Et_2O) to give **2.56** (36.2 mg, 0.188 mmol, 74 %) as a colorless oil.

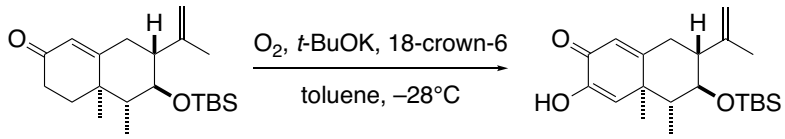
TLC: R_f = 0.46 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{24}$ = +181.2° (c = 0.52, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3400, 2971, 2881, 1648, 1622, 1585, 1445, 1416, 1356, 1318, 1272, 1233, 1203, 1130, 1034, 1001, 948, 883, 756, 640, 577, 530 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.18 (dd, *J* = 10.0, 1.5, 1H), 6.15 (dd, *J* = 9.9, 1.5, 1H), 5.76 (s, 1H), 4.08 (d, *J* = 9.8, 1H), 2.54 (ddd, *J* = 17.9, 14.6, 5.4, 1H), 2.43 (dddd, *J* = 18.0, 5.2, 2.3, 1.0, 1H), 2.05 (ddd, *J* = 13.3, 5.4, 2.3, 1H), 1.77 (td, *J* = 13.9, 5.1, 1H), 1.54 (dq, *J* = 9.6, 6.8, 1H), 1.12 (d, *J* = 6.8, 3H), 1.10 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 199.5, 162.0, 140.1, 128.5, 124.9, 71.4, 47.7, 37.5, 33.9, 33.3, 16.3, 10.4. **HRMS** (ESI) Exact mass calculated for $C_{12}H_{17}O_2^+$ $[M+H]^+$: 193.12231, found: 193.12258.



2.56 **2.57**, 86 %

(1*R*,8a*R*)-1,8a-Dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (2.57): $NaHCO_3$ (546 mg, 6.50 mmol, 5.0 equiv.) and DMP (827 mg, 1.95 mmol, 1.5 equiv.) were added sequentially to a solution of **2.56** (250 mg, 1.30 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) at 0°C. The mixture was stirred at this temperature for 1 h, before sat. aq. $Na_2S_2O_3$ solution was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x) and the combined organic layers were washed with sat. aq. $NaHCO_3$ solution, H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/ Et_2O 1:1) to give **2.57** (212 mg, 1.11 mmol, 86 %) as a yellowish solid.

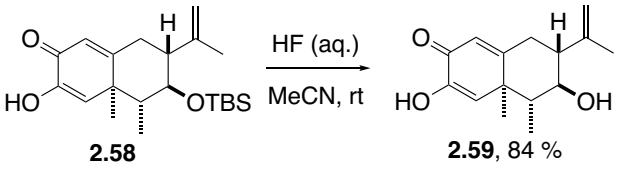
M.p. = 105.7 – 107.3°C. TLC: R_f = 0.19 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{25}$ = +256.1° (c = 0.45, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2971. 2947, 2874, 1656, 1570, 1451, 1417, 1355, 1328, 1267, 1231, 1206, 1139, 1103, 1065, 1025, 947, 885, 833, 784, 757, 724, 654 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.00 (d, *J* = 9.8, 1H), 6.23 (d, *J* = 9.9, 1H), 6.05 (d, *J* = 0.9, 1H), 2.58 (q, *J* = 6.8, 1H), 2.56 – 2.51 (m, 2H), 2.16 – 2.09 (m, 1H), 2.00 (td, *J* = 12.8, 7.3, 1H), 1.16 (s, 3H), 1.15 (d, *J* = 6.8, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 200.0, 198.8, 159.5, 142.4, 132.3, 129.2, 52.2, 40.0, 34.5, 33.5, 18.3, 7.1. **HRMS** (ESI) Exact mass calculated for $C_{12}H_{15}O_2^+$ $[M+H]^+$: 191.10666, found: 191.10685.



2.42 **2.58**, 81 %

(4a*S*,5*R*,6*S*,7*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-4a,5-dimethyl-7-(prop-1-en-2-yl)-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one (2.58): To a solution of **2.42** (49.8 mg, 0.143 mmol, 1.0 equiv.) and 18-crown-6 (56.7 mg, 0.214 mmol, 1.5 equiv.) in toluene (5.0 mL) at –28°C (dry-ice/acetone bath) was added *t*-BuOK (64.2 mg, 0.572 mmol, 4.0 equiv.). The solution turned orange and O_2 was bubbled through the reaction mixture for 15 min. The yellow solution was then allowed to stir under an O_2 atmosphere (1 atm) for further 15 min. After TLC showed full consumption of the starting materials, the mixture was quenched by addition of aq. HCl solution (0.1 M, pH = 5) and extracted with Et_2O (3 x). The combined organic layers were washed with sat. aq. $NaHCO_3$ solution, H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 3:1) to give **2.58** (42.0 mg, 0.116 mmol, 81 %) as a yellowish oil.

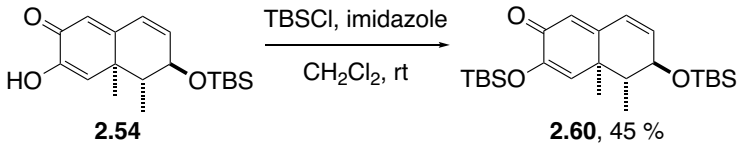
TLC: R_f = 0.72 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{25}$ = –55.0° (c = 1.34, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3379, 2953, 2631, 1645, 1431, 1384, 1229, 1073, 886, 835, 774, 679 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.31 (s, 1H), 6.27 (s, 1H), 6.18 (d, *J* = 1.4 Hz, 1H), 4.88 (s, 2H), 3.62 (t, *J* = 9.7 Hz, 1H), 2.59 (td, *J* = 13.6, 1.5 Hz, 1H), 2.32 (dd, *J* = 13.5, 4.3 Hz, 1H), 2.21 (ddd, *J* = 13.9, 9.9, 4.3 Hz, 1H), 1.75 (s, 3H), 1.45 (dq, *J* = 9.5, 6.8 Hz, 1H), 1.19 (s, 3H), 1.18 (d, *J* = 6.7 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 181.6, 170.5, 146.3, 145.2, 123.5, 121.4, 114.3, 74.1, 55.5, 48.6, 44.2, 37.2, 26.3 (3C), 20.5, 20.0, 18.6, 13.6, -2.7, -3.4. **HRMS** (ESI) Exact mass calculated for $C_{21}H_{34}NaO_3Si^+$ $[M+Na]^+$: 385.2169, found: 385.2170.



2.58 **2.59**, 84 %

(4a*S*,5*R*,6*S*,7*R*)-3,6-Dihydroxy-4a,5-dimethyl-7-(prop-1-en-2-yl)-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one (2.59): To a solution of **2.58** (8.7 mg, 24 µmol, 1.0 equiv.) in MeCN (0.5 mL) was added a solution of HF (48 % in H_2O, 10 µL, 0.24 mmol, 10 equiv.). The mixture was stirred for 4 h at rt and then quenched by addition of sat. aq. $NaHCO_3$ solution. The mixture was extracted with Et_2O (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 1:1) to give **2.59** (5.0 mg, 20 µmol, 84 %) as a colorless oil.

TLC: R_f = 0.27 (SiO_2, pentane/Et_2O 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.31 (s, 1H), 6.30 (s, 1H), 6.22 (d, *J* = 1.3, 1H), 5.01 (p, *J* = 1.7, 1H), 4.94 (dd, *J* = 1.7, 0.9, 1H), 3.51 (td, *J* = 10.0, 2.3, 1H), 2.60 (td, *J* = 13.4, 1.5, 1H), 2.39 (dd, *J* = 13.4, 4.2, 1H), 2.16 (ddd, *J* = 13.9, 10.2, 4.2, 1H), 1.79 (s, 3H), 1.76 (d, *J* = 2.7, 1H), 1.51 – 1.39 (m, 1H), 1.27 (d, *J* = 6.7, 3H), 1.21 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 181.6, 169.7, 146.3, 144.6, 123.4, 122.2, 115.0, 70.9, 55.6, 47.1, 44.1, 36.0, 20.0, 18.8, 12.4. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{20}NaO_3^+$ $[M+Na]^+$: 271.1305, found: 271.1305.

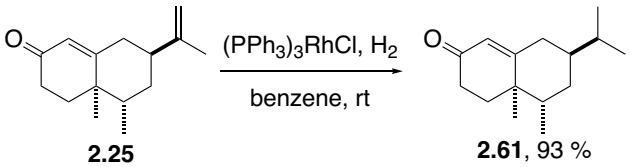


2.54 **2.60**, 45 %

(4a*S*,5*R*,6*R*)-3,6-bis((*tert*-Butyldimethylsilyl)oxy)-4a,5-dimethyl-5,6-dihydronaphthalen-2(4a*H*)-one (2.60): To a solution of **2.54** (10.0 mg, 31 µmol, 1.0 equiv.) in CH_2Cl_2 (0.6 mL) was added imidazole (8.5 mg, 0.125 mmol, 4.0 equiv.) and TBSCl (9.4 mg, 62 µmol, 2.0 equiv.) and the mixture was stirred for 2 h at rt, before it was poured into H_2O and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude ^{1}H NMR spectra showed clean conversion and the residue was subjected to flash column chromatography (pentane/Et_2O 10:1) to give **2.60** (6.1 mg, 14 µmol, 45 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.30 (s, 1H), 6.28 (d, *J* = 8.7, 1H), 6.09 (s, 1H), 6.01 (d, *J* = 10.0, 1H), 4.02 (dd, *J* = 9.1, 2.5, 1H), 1.70 – 1.61 (m, 1H), 1.19 (d, *J* = 6.7, 3H), 1.10 (s, 3H),

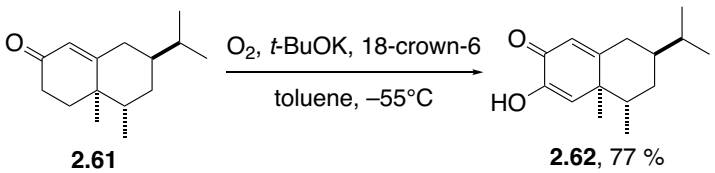
0.96 (s, 9H), 0.91 (s, 9H), 0.20 (s, 3H), 0.16 (s, 3H), 0.13 (s, 3H), 0.13 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 182.5, 160.8, 148.1, 138.4, 131.5, 127.3, 124.2, 71.9, 45.7, 43.3, 25.9 (3C), 25.9 (3C), 21.4, 18.7, 18.2, 11.9, -3.8, -4.3, -4.4, -4.5.



2.25 **2.61**, 93 %

(4a*R*,5*S*,7*S*)-7-Isopropyl-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.61): Wilkinsons's catalyst (10.6 mg, 11.5 µmol, 2.5 mol%) was added to a solution of the octalone **2.25** (100 mg, 0.458 mmol, 1.0 equiv.) in benzene (2.0 ml) under an H_2 atmosphere (1 atm) and the mixture was stirred at rt o.n. Reaction control by TLC showed remaining starting material and additional Wilkinson's catalyst (10.6 mg, 11.5 µmol, 2.5 mol%) was added. After stirring was continued for 4 h, the mixture was concentrated. The obtained residue was purified by flash column chromatography (pentane/Et_2O 3:1) to give the isopropylated compound **2.61** (93.7 mg, 0.425 mmol, 93 %) as pale orange crystals.

M.p. = 69 – 72°C. TLC: R_f = 0.57 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = +122.5° (c = 0.56, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2960, 2874, 2362, 1674, 1616, 1460, 1232, 952, 857. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.74 (s, 1H), 2.49 – 2.30 (m, 4H), 2.04 (ddd, *J* = 13.4, 5.1, 3.0, 1H), 1.77 – 1.46 (m, 5H), 1.45 – 1.37 (m, 1H), 1.12 (s, 3H), 0.90 – 0.84 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 199.6, 170.6, 125.7, 41.8, 39.0, 37.4, 36.4, 35.9, 34.2, 33.0, 27.3, 21.2, 20.8, 16.5, 15.5. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{25}O^+$ $[M+H]^+$: 221.1900, found: 221.1900.

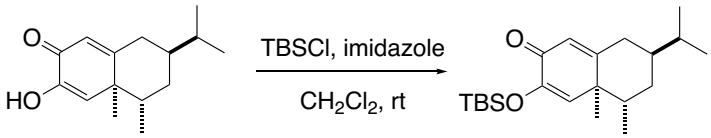


2.61 **2.62**, 77 %

(4a*S*,5*S*,7*S*)-3-Hydroxy-7-isopropyl-4a,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one (2.62): To a solution of the isopropylated enone **2.61** (200 mg, 0.908 mmol, 1.0 equiv.) and 18-crown-6 (360 mg, 1.36 mmol, 1.5 equiv.) in toluene (10 mL) at –60°C (dry-ice/acetone bath) was added *t*-BuOK (204 mg, 1.82 mmol, 2.0 equiv.) to form a yellow solution. O_2 was

bubbled through this solution for 3 min, before it was allowed to stir under an O_2 atmosphere (1 atm) at –55°C for 1.5 h. The mixture was acidified to pH = 1 by addition of aqueous HCl (0.1 M), stirred for further 30 min and extracted with Et_2O (3 x). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 3:1) to give the diosphenol **2.62** (163 mg, 0.696 mmol, 77 %) as a brownish solid.

M.p. = 68 – 70°C. TLC: $\boldsymbol{R_f}$ = 0.70 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = –75.9° (c = 0.10, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3380, 2963, 2965, 2871, 2362, 1632, 1459, 1417, 1373, 1302, 1203, 909, 875, 618 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.33 (s, 1H), 6.32 (s, 1H), 6.18 (s, 1H), 2.54 – 2.50 (m, 2H), 1.70 – 1.64 (m, 1H), 1.64 – 1.48 (m, 3H), 1.44 – 1.34 (m, 1H), 1.14 (s, 3H), 1.02 (d, *J* = 6.3, 3H), 0.89 (d, *J* = 6.5, 3H), 0.81 (d, *J* = 6.6, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 181.6, 171.3, 146.4, 124.5, 123.0, 44.5, 43.8, 37.2, 35.7, 32.3, 26.4, 21.2, 20.8, 18.7, 16.5. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{23}O_2^+$ $[M+H]^+$: 235.1691, found: 235.1693.

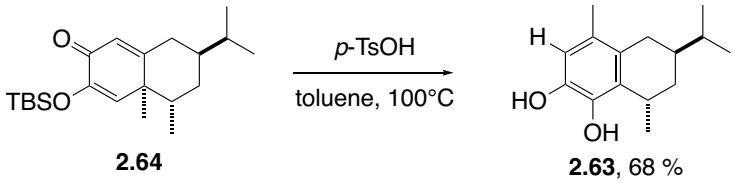


2.62 **2.64**, 82 %

(4a*S*,5*S*,7*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-7-isopropyl-4a,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one (2.64): To a solution of diosphenol **2.62** (105 mg, 0.448 mmol, 1.0 equiv.) and imidazole (122 mg, 1.79 mmol, 4.0 equiv.) in CH_2Cl_2 (5.0 ml) was added TBSCl (135 mg, 0.896 mmol, 2.0 equiv.) and the mixture was stirred for 2.5 h at rt. The reaction mixture was poured into H_2O and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 10:1) to give the TBS protected diosphenol **2.64** (128 mg, 0.368 mmol, 82 %) as a colorless solid.

M.p. = 50 – 53°C. TLC: $\boldsymbol{R_f}$ = 0.81 (SiO_2, pentane/Et_2O 5:1). **Optical rotation**: $[\alpha]_D^{24}$ = –46.4° (c = 0.57, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2956, 2930, 2894, 2858, 2362, 1664, 1612, 1461, 1250, 1195, 871, 838, 783 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.29 (s, 1H), 6.04 (t, *J* = 1.0, 1H), 2.49 – 2.45 (m, 2H), 1.70 – 1.47 (m, 4H), 1.42 (dtd, *J* = 12.8, 6.4, 4.1, 1H), 1.13 (s, 3H), 1.00 (d, *J* = 6.3, 3H), 0.96 (s, 9H), 0.89 (d, *J* = 6.4, 3H), 0.82 (d, *J* = 6.5, 3H), 0.19 (s, 3H), 0.18 (s,

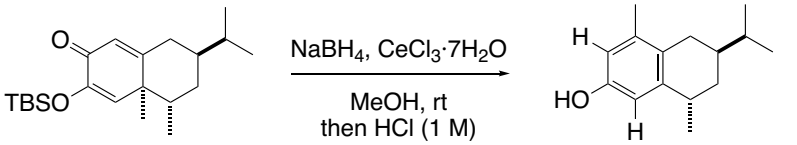
3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 182.8, 166.7, 147.5, 133.9, 125.6, 44.5, 43.5, 36.9, 35.0, 32.4, 26.3, 25.9 (3C), 21.3, 20.8, 18.7, 18.6, 16.4, -4.3, -4.4. **HRMS** (ESI) Exact mass calculated for $C_{21}H_{37}O_2Si^+$ $[M+H]^+$: 349.2559, found: 349.2557.



2.64 **2.63**, 68 %

(6*S*,8*S*)-6-Isopropyl-4,8-dimethyl-5,6,7,8-tetrahydronaphthalene-1,2-diol (2.63): To a solution of **2.64** (20 mg, 57 µmol, 1.0 equiv.) in toluene (2.0 ml) was added *p*-TsOH·H_2O (2.2 mg, 12 µmol, 0.2 equiv.) and the mixture was stirred at 80°C for 3 h. Almost no conversion was monitored by TLC (pentane/Et_2O 5:1) and the mixture was heated to 100°C o.n. Additional *p*-TsOH·H_2O (8.7 mg, 46 µmol, 0.8 equiv.) was added and the mixture was diluted with Et_2O and quenched by addition of sat. aq. $NaHCO_3$ solution after 2.5 h at 100°C. The layers were separated and the aqueous layer was extracted with Et_2O (2 x). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 4:1) to give **2.63** (9.1 mg, 39 µmol, 68 %) as a colorless oil.

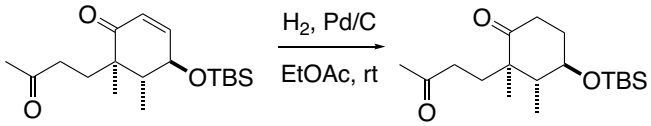
TLC: $\boldsymbol{R_f}$ = 0.17 (SiO_2, pentane/Et_2O 5:1). **Optical rotation**: $[\alpha]_D^{23}$ = –22.7° (c = 0.46, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3437, 2957, 2930, 2872, 1816, 1468, 1385, 1289, 1176, 919 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.57 (s, 1H), 4.98 (s, 1H), 4.78 (s, 1H), 3.20 (p, *J* = 6.6, 6.0, 1H), 2.64 (ddd, *J* = 16.8, 5.2, 2.0, 1H), 2.12 (s, 3H), 2.15 – 2.06 (m, 1H), 1.76 – 1.70 (m, 1H), 1.70 – 1.63 (m, 1H), 1.63 – 1.56 (m, 1H), 1.44 (td, *J* = 12.5, 5.3, 1H), 1.26 (d, *J* = 7.0, 3H), 1.02 – 0.95 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 140.2, 139.4, 129.4, 128.3, 128.2, 114.6, 34.5, 33.0, 32.8, 30.8, 28.3, 20.9, 19.9, 19.8, 19.3. **MS** (EI) Mass calculated for $C_{15}H_{22}O_2$ $[M]^+$: 234.16, found: 234.22.



2.64 **2.66**, 38 %
4:3 (**2.66**/**2.64**, ^{1}H NMR)

(6*S*,8*S*)-6-Isopropyl-4,8-dimethyl-5,6,7,8-tetrahydronaphthalen-2-ol (2.66): To a stirred solution of **2.64** (10 mg, 29 µmol, 1.0 equiv.) and $CeCl_3 \cdot 7H_2O$ (10.7 mg, 29 µmol, 1.0 equiv.) in MeOH (1.0 mL) at 0 °C was added $NaBH_4$ (2.2 mg, 57 µmol, 2.0 equiv.). The mixture was allowed to warm up to rt and stirred for 2 h. Aqueous HCl (1 M) was added and the mixture was extracted with Et_2O (3 x). The combined organic layers were washed with brine, dried over $NaSO_4$, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 4:1) to give **2.66** (2.4 mg, 11 µmol, 38 %) as a colorless solid.

TLC: R_f = 0.47 (SiO_2, pentane/Et_2O 3:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.50 (d, *J* = 2.8, 1H), 6.48 (d, *J* = 2.7, 1H), 4.39 (s, 1H), 2.95 (dddd, *J* = 13.0, 7.2, 4.8, 2.3, 1H), 2.62 (ddd, *J* = 16.5, 5.0, 1.8, 1H), 2.18 (s, 3H), 2.12 (dd, *J* = 16.5, 10.6, 1H), 1.67 – 1.62 (m, 2H), 1.62 – 1.57 (m, 1H), 1.55 – 1.48 (m, 1H), 1.24 (d, *J* = 7.2, 3H), 0.97 (t, *J* = 6.4, 6H). **^{13}C NMR** (126 MHZ, $CDCl_3$, DEPT 135/HMBC) δ = 152.8, 143.7, 138.0, 127.5, 114.5, 112.6, 35.2, 33.2, 33.0, 32.4, 30.6, 24.0, 19.8 (2C), 19.8. **MS** (EI) Mass calculated for $C_{15}H_{22}O$ $[M]^+$: 218.17, found: 218.22.

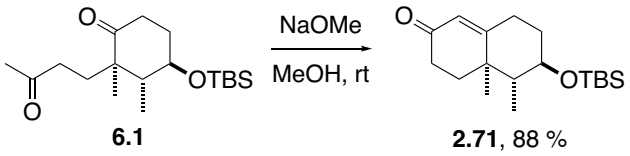


2.34 **6.1**, quant.

(2*R*,3*R*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-2,3-dimethyl-2-(3-oxobutyl)cyclohexan-1-one (6.1): A mixture of **2.34** (200 mg, 0.616 mmol, 1.0 equiv.) and 5 % Pd/C (32.8 mg, 2.5 mol%) in EtOAc (10 mL) was stirred under an H_2 atmosphere (1 atm) for 2 h. The mixture was then filtered through a short pad of Celite (rinsed with Et_2O) and the solvent was removed under reduced pressure to give **6.1** (202 mg, 0.616 mmol, quant.) as a colorless oil.

TLC: R_f = 0.74 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = –4.9° (c = 0.40, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2932, 2888, 2858, 1708, 1463, 1430, 1361, 1292, 1254, 1099, 1070, 988, 954, 884, 835, 775, 661, 629 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.79 (ddd, *J* = 9.0, 4.2 Hz, 1H), 2.55 – 2.35 (m, 3H), 2.32 – 2.22 (m, 1H), 2.13 (s, 3H), 2.12 – 2.06 (m, 1H), 2.01 – 1.92 (m, 1H), 1.78 – 1.61 (m, 3H), 1.02 (s, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.09

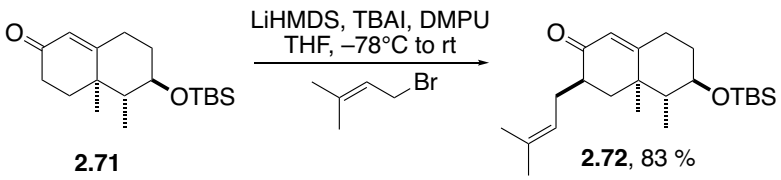
(s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 214.3, 208.9, 71.7, 50.6, 44.7, 38.9, 35.9, 33.8, 30.1, 29.6, 26.0 (3C), 20.5, 18.2, 12.6, -4.1, -4.6. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{35}O_3Si^+$ $[M+H]^+$: 327.2350, found: 327.2348; for $C_{18}H_{34}NaO_3Si^+$ $[M+Na]^+$: 349.2169, found: 349.2169.



6.1 **2.71**, 88 %

(4a*R*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydro-naphthalen-2(3*H*)-one (2.71): To a solution of **6.1** (3.53 g, 10.8 mmol, 1.0 equiv.) in MeOH (56.0 mL) was added a solution of NaOMe (0.5 M in MeOH, 28.1 mL, 14.0 mmol, 1.3 equiv.) and the mixture was stirred for 4 h at rt. H_2O was added and the resulting turbid mixture was extracted with Et_2O (3 x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The slurry was again partitioned between H_2O and Et_2O and separated. After extraction of the aqueous layer with Et_2O (2 x), the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 3:1) to give **2.71** (2.92 g, 9.46 mmol, 88 %) as a colorless solid.

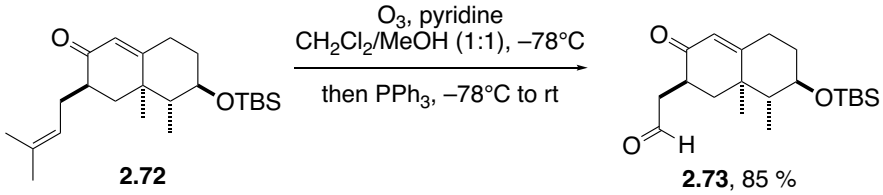
M.p. = 37.1 – 39.9°C. TLC: $\boldsymbol{R_f}$ = 0.67 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = +78.7° (c = 0.57, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2951, 2858, 1678, 1621, 1463, 1386, 1359, 1253, 1185, 1073, 1019, 948, 889, 867, 834, 775, 683 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.74 (s, 1H), 3.57 (ddd, *J* = 10.5, 4.4 Hz, 1H), 2.46 – 2.33 (m, 3H), 2.28 (ddd, *J* = 14.9, 4.7, 2.8 Hz, 1 H), 2.08 – 1.98 (m, 2H), 1.73 (ddd, *J* = 13.7, 5.4 Hz, 1H), 1.45 (dddd, *J* = 14.6, 12.0, 10.7, 4.4 Hz, 1H), 1.36 (dq, *J* = 10.0, 6.6 Hz, 1H), 1.11 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 199.6, 169.4, 124.3, 72.0, 50.1, 39.3, 36.0, 35.9, 33.6, 31.5, 26.0 (3C), 18.2, 17.4, 11.2, -3.9, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{33}O_2Si^+$ $[M+H]^+$: 309.2244, found: 309.2246; for $C_{18}H_{32}NaO_2Si^+$ $[M+Na]^+$: 331.2064, found: 331.2065.



2.71 **2.72**, 83 %

(3*R*,4a*R*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-4a,5-dimethyl-3-(3-methylbut-2-en-1-yl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.72): To a cooled (–78°C) solution of **2.71** (2.00 g, 6.48 mmol, 1.0 equiv.) in THF (100 mL) were added sequentially a solution of LiHMDS (1.0 M in THF, 9.72 mL, 9.72 mmol, 1.5 equiv.) and DMPU (3.13 mL, 25.9 mmol, 4.0 equiv.) dropwise *via* syringe. The resulting solution was stirred for 2 h at –78°C, before prenyl bromide (2.99 mL, 25.9 mmol, 4.0 equiv.) and TBAI (9.57 g, 25.9 mmol, 4.0 equiv.) were added. The mixture was allowed to slowly warm up to rt and stirred o.n., before it was quenched by addition of sat. aq. NH_4Cl solution and diluted with H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/ Et_2O 6:1) to give **2.72** (2.25 g, 5.38 mmol, 83 %, 90 % purity according to ^1H NMR spectrum) as a colorless oil.

TLC: R_f = 0.76 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{25}$ = +56.0° (c = 0.51, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3676, 2956, 2930, 2859, 1675, 1627, 1461, 1381, 1253, 1072, 889, 835, 775 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.71 (d, *J* = 1.7 Hz, 1H), 5.09 (dddd, *J* = 9.1, 6.7, 2.7, 1.3 Hz, 1H), 3.55 (td, *J* = 10.5, 4.4 Hz, 1H), 2.63 – 2.52 (m, 1H), 2.43 – 2.23 (m, 3H), 2.08 – 1.96 (m, 3H), 1.70 (s, 3H), 1.61 (s, 3H), 1.49 – 1.27 (m, 3H), 1.11 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 200.9, 168.1, 133.5, 124.2, 121.9, 71.9, 50.6, 42.0, 42.0, 39.9, 35.8, 31.1, 27.6, 26.0, 26.0 (3C), 18.2, 18.0, 17.6, 11.1, -3.9, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{23}H_{41}O_2Si^+$ $[M+H]^+$: 377.2870, found: 377.2873; for $C_{23}H_{40}NaO_2Si^+$ $[M+Na]^+$: 399.2690, found: 399.2689.

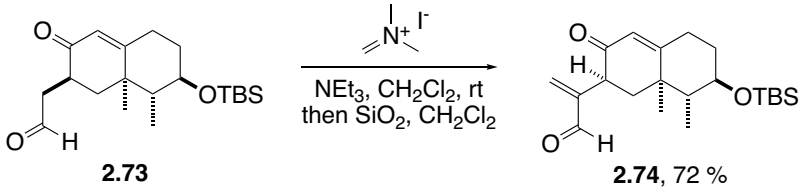


2.72 **2.73**, 85 %

2-((2*S*,7*R*,8*R*,8a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)acetaldehyde (2.73): A solution of **2.72** (1.0 g, 2.65 mmol, 1.0 equiv.), pyridine (0.85 mL, 10.6 mmol, 4.0 equiv.) and Sudan III (spatula tip) in

CH_2Cl_2/MeOH (100 mL, 1:1) was cooled to –78°C and O_3 was bubbled through the solution until the red color disappeared. The reaction was purged with O_2 and Ar, before PPh_3 (1.39 g, 5.30 mmol, 2.0 equiv.) was added and the mixture was allowed to warm up to rt. After stirring for 2 h at rt, the solvent was removed by evaporation and the residue was subjected to flash column chromatography (pentane/Et_2O 3:1) to give **2.73** (788 mg, 2.25 mmol, 85 %) as a colorless solid.

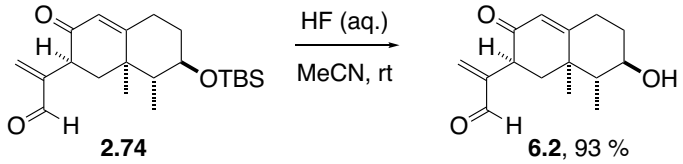
M.p. = 58.2 – 60.3°C. TLC: $\boldsymbol{R_f}$ = 0.53 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{25}$ = +40.4° (c = 0.33, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2931, 2886, 2857, 1724, 1673, 1625, 1463, 1386, 1253, 1186, 1076, 1007, 888, 834, 774, 691 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.86 (t, *J* = 1.2 Hz, 1H), 5.76 (d, *J* = 1.7 Hz, 1H), 3.56 (ddd, *J* = 10.5, 4.4 Hz, 1H), 3.08 – 2.96 (m, 2H), 2.41 (tdd, *J* = 14.5, 5.1, 1.9 Hz, 1H), 2.36 – 2.26 (m, 2H), 2.08 – 1.96 (m, 2H), 1.56 – 1.27 (m, 3H), 1.19 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 201.0, 199.1, 169.1, 123.3, 71.8, 50.5, 43.8, 42.9, 40.2, 37.5, 35.8, 31.3, 26.0 (3C), 18.2, 17.5, 11.0, -3.9, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{20}H_{35}O_3Si^+$ $[M+H]^+$: 351.2350, found: 351.2353; for $C_{20}H_{34}NaO_3Si^+$ $[M+Na]^+$: 373.2169, found: 373.2174.



2-((2*S*,7*R*,8*R*,8a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)acrylaldehyde (2.74): Eschenmoser's salt (408 mg, 2.16 mmol, 2.5 equiv.) was added to a solution of **2.73** (303 mg, 0.864 mmol, 1.0 equiv.) and Et_3N (2.43 mL, 17.3 mmol, 20 equiv.) in CH_2Cl_2 (150 mL) at rt. The mixture was stirred for 3.5 h and then quenched by addition of H_2O and acidified with aq. HCl solution (1.0 M, pH = 1). After stirring was continued for 30 min, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in CH_2Cl_2 and SiO_2 was added. After stirring for 1 h, the mixture was concentrated and purified by flash column chromatography (pentane/Et_2O 1:1) to give **2.74** (227 mg, 0.625 mmol, 72 %) as a colorless oil.

TLC: $\boldsymbol{R_f}$ = 0.43 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = +12.0° (c = 0.27, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2932, 2885, 2857, 2361, 1745, 1677, 1626, 1463, 1363, 1326, 1252, 1186,

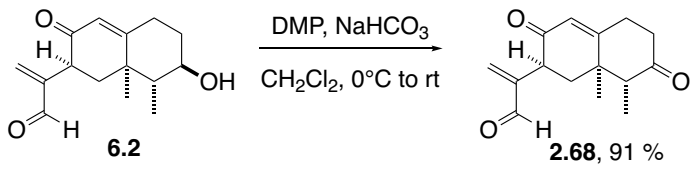
1131, 1078, 956, 888, 835, 775 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.57 (s, 1H), 6.33 (s, 1H), 6.23 (s, 1H), 5.79 (d, *J* = 1.7 Hz, 1H), 3.63 (dd, *J* = 14.2, 4.8 Hz, 1H), 3.57 (dd, *J* = 10.5, 4.3 Hz, 1H), 2.43 (tdd, *J* = 14.4, 5.0, 1.9 Hz, 1H), 2.32 (ddd, *J* = 14.9, 4.6, 2.7 Hz, 1H), 2.04 (ddt, *J* = 9.4, 7.4, 3.8 Hz, 1H), 1.99 (dd, *J* = 13.0, 4.8 Hz, 1H), 1.90 (t, *J* = 13.6 Hz, 1H), 1.47 (dddd, *J* = 14.2, 12.5, 10.8, 4.5 Hz, 1H), 1.38 (dq, *J* = 10.0, 6.8 Hz, 1H), 1.20 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 197.1, 193.5, 168.6, 148.5, 136.1, 123.9, 71.8, 50.4, 42.1, 41.9, 40.1, 35.7, 31.2, 26.0 (3C), 18.2, 17.4, 11.1, -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{21}H_{35}O_3Si^+$ $[M+H]^+$: 363.2350, found: 363.2353; for $C_{21}H_{34}NaO_3Si^+$ $[M+Na]^+$: 385.2169, found: 385.2174.



2.74 **6.2**, 93 %

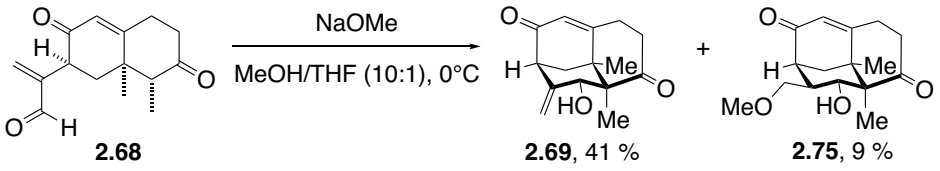
2-((2*S*,7*R*,8*R*,8a*R*)-7-Hydroxy-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)acrylaldehyde (6.2): To a solution of **2.74** (23.5 mg, 65 µmol, 1.0 equiv.) in MeCN (2.5 mL) was added a solution of HF (48 % in H_2O, 27.3 µL, 0.648 mmol, 10 equiv.). The mixture was stirred for 2 h, before it was quenched with sat. aq. $NaHCO_3$ solution. The mixture was extracted with Et_2O (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by filtration through a short plug of SiO_2 (eluted with Et_2O) to give **6.2** (15.0 mg, 60 µmol, 93 %) as a colorless oil.

TLC: R_f = 0.24 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{25}$ = +51.2° (c = 0.76, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3434, 2972, 2941, 2880, 2363, 1668, 1624, 1445, 1326, 1242, 1196, 1034, 956 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.57 (s, 1H), 6.35 (d, *J* = 0.7 Hz, 1H), 6.24 (s, 1H), 5.82 (d, *J* = 1.7 Hz, 1H), 3.68 – 3.57 (m, 2H), 2.47 (dddd, *J* = 15.0, 14.1, 5.1, 1.9 Hz, 1H), 2.37 (ddd, *J* = 15.0, 4.7, 2.6 Hz, 1H), 2.17 (dtd, *J* = 12.2, 4.8, 2.7 Hz, 1H), 2.01 (dd, *J* = 13.0, 4.9 Hz, 1H), 1.93 (t, *J* = 13.5 Hz, 1H), 1.53 – 1.40 (m, 2H), 1.35 (dq, *J* = 10.3, 6.8 Hz, 1H), 1.21 (s, 3H), 1.05 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 196.9, 193.5, 167.9, 148.4, 136.3, 124.3, 71.2, 50.2, 42.1, 41.9, 40.1, 35.3, 31.2, 17.4, 10.5. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{21}O_3^+$ $[M+H]^+$: 249.1485, found: 249.1482; for $C_{15}H_{20}NaO_3^+$ $[M+Na]^+$: 271.1305, found: 281.1307.



2-((2*S*,8*R*,8a*R*)-8,8a-Dimethyl-3,7-dioxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)acrylaldehyde (2.68): $NaHCO_3$ (40.1 mg, 0.48 mmol, 8.0 equiv.) and DMP (50.6 mg, 0.12 mmol, 2.0 equiv.) were added sequentially to a solution of **6.2** (14.8 mg, 60 µmol, 1.0 equiv.) in CH_2Cl_2 (1.5 mL) at 0°C. The mixture was warmed up to rt and stirred for 30 min, before sat. aq. $Na_2S_2O_3$ was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (Et_2O) to give **2.68** (13.4 mg, 54 µmol, 91 %) as a colorless solid.

M.p. = 84.2°C (decomposed). TLC: R_f = 0.45 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{24}$ = +26.7° (c = 0.66, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2973, 2361, 1715, 1676, 1625, 1445, 1324, 1181, 960, 920, 867 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.56 (s, 1H), 6.37 (s, 1H), 6.26 (s, 1H), 5.97 (s, 1H), 3.57 (dd, *J* = 14.3, 4.5 Hz, 1H), 2.86 – 2.73 (m, 2H), 2.65 – 2.49 (m, 3H), 2.21 (dd, *J* = 14.2, 13.1 Hz, 1H), 1.97 (dd, *J* = 13.0, 4.6 Hz, 1H), 1.16 (s, 3H), 1.02 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 209.5, 196.3, 193.3, 164.5, 148.0, 136.6, 125.1, 53.8, 43.2, 42.9, 41.4, 39.8, 32.1, 18.1, 7.2. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{19}O_3^+$ $[M+H]^+$: 247.1329, found: 247.1325; for $C_{15}H_{18}NaO_3^+$ $[M+Na]^+$: 269.1148, found: 269.1149.



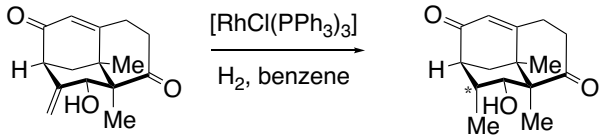
To a solution of **2.68** (131 mg, 0.53 mmol, 1.0 equiv.) in MeOH/THF (29 mL, 10:1) at 0°C was added dropwise NaOMe (0.5 M in MeOH, 1.28 mL, 0.64 mmol, 1.2 equiv.) and the mixture was stirred for 2 h at this temperature. H_2O and EtOAc were added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (Et_2O) to give **2.69** (54.1 mg, 0.22 mmol, 41 %) as a colorless solid and **2.75** (12.7 mg, 0.05 mmol, 9 %) as a beige solid.

(1*R*,7*S*,8a*S*,10*R*)-10-Hydroxy-1,8a-dimethyl-9-methylene-1,3,4,7,8,8a-hexahydro-1,7-ethanonaphthalene-2,6-dione (2.69):

M.p. = 169.2 – 175.3°C. TLC: R_f = 0.39 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{24}$ = +79.8° (c = 0.65, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3418, 2953, 1705, 1673, 1619, 1464, 1446, 1386, 1329, 1285, 1237, 1167, 1106, 1069, 1049, 1011, 995, 918, 892, 862, 772, 731, 565, 537 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.17 (s, 1H), 5.22 (s, 1H), 5.19 (s, 1H), 4.78 (dt, *J* = 7.2, 2.3, 1H), 3.32 (t, *J* = 2.5, 1H), 2.96 (tdd, *J* = 12.1, 7.4, 1.5, 1H), 2.82 (ddd, *J* = 16.0, 12.1, 8.0, 1H), 2.70 (ddd, *J* = 16.0, 7.4, 1.3, 1H), 2.62 (dd, *J* = 12.1, 8.0, 1H), 2.01 (dd, *J* = 13.5, 2.7, 1H), 1.96 (dd, *J* = 13.6, 3.4, 1H), 1.90 (d, *J* = 7.2, 1H), 1.11 (s, 3H), 1.03 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 209.5, 197.4, 165.9, 140.9, 126.4, 112.9, 72.0, 59.8, 54.0, 42.1, 38.6, 35.6, 30.7, 22.8, 7.9. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{19}O_3^+$ $[M+H]^+$: 247.1329, found: 247.1328; for $C_{15}H_{18}NaO_3^+$ $[M+Na]^+$: 269.1148, found: 269.1148.

(1*R*,7*S*,8a*S*,9*R*,10*R*)-10-Hydroxy-9-(methoxymethyl)-1,8a-dimethyl-1,3,4,7,8,8a-hexahydro-1,7-ethanonaphthalene-2,6-dione (2.75):

M.p. = 100.7 – 103.8°C. TLC: R_f = 0.43 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{24}$ = –83.1° (c = 0.49, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3455, 2923, 1704, 1668, 1448, 1387, 1332, 1283, 1169, 1109, 1040, 963, 887, 749, 559 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.13 (s, 1H), 4.25 (dd, *J* = 10.3, 1.5, 1H), 3.68 (dd, *J* = 9.6, 3.9, 1H), 3.59 (d, *J* = 1.5, 1H), 3.35 (dd, *J* = 9.3, 7.6, 1H), 3.33 (s, 3H), 2.95 – 2.80 (m, 2H), 2.71 – 2.62 (m, 1H), 2.60 – 2.53 (m, 2H), 2.04 – 1.91 (m, 3H), 1.18 (s, 3H), 1.09 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 209.9, 198.9, 166.1, 127.3, 76.2, 74.2, 59.3, 58.3, 45.7, 41.5, 38.6, 38.4, 34.3, 30.8, 23.1, 8.5. **HRMS** (ESI) Exact mass calculated for $C_{16}H_{23}O_4^+$ $[M+H]^+$: 279.15909, found: 279.15926.

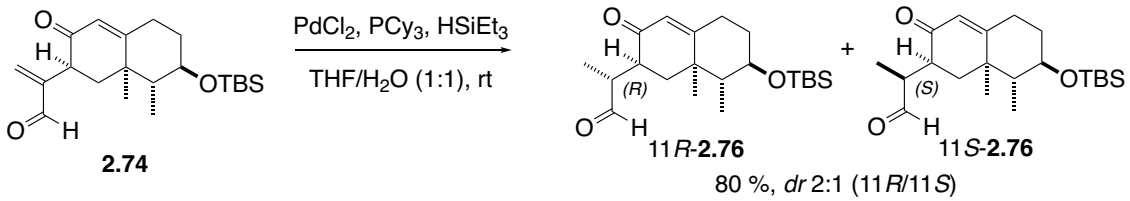


2.69 11*R*-**2.70**, 80 %, *dr* 20:1

(1*R*,7*S*,8a*S*,9*R*,10*R*)-10-Hydroxy-1,8a,9-trimethyl-1,3,4,7,8,8a-hexahydro-1,7-ethanonaphthalene-2,6-dione (11*R*-**2.70):** A solution of **2.69** (30.0 mg, 0.122 mmol, 1.0 equiv.) and Wilkinson's catalyst (4.21 mg, 6.1 µmol, 5 mol%) in benzene (2.0 mL) was stirred under an H_2 atmosphere (1 atm) for 2 h. The solvent was evaporated and the residue was subjected to flash

column chromatography (Et_2O) to give 11*R*-**2.70** (24.3 mg, 98 µmol, 80 %, *dr* 20:1) as a colorless solid.

M.p. = 133.1 – 138.3°C. TLC: R_f = 0.26 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{24}$ = –83.4° (c = 1.10, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3420, 2922, 1701, 1657, 1460, 1387, 1297, 1166, 1109, 1085, 1037, 1009, 990, 889, 743, 568, 498 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.19 (s, 1H), 4.17 (d, *J* = 6.4, 1H), 2.93 (dddd, *J* = 12.6, 11.6, 8.0, 1.4, 1H), 2.79 – 2.72 (m, 1H), 2.69 (ddd, *J* = 16.8, 8.1, 2.1, 1H), 2.55 (ddd, *J* = 12.3, 7.6, 2.0, 1H), 2.50 (q, *J* = 2.8, 1H), 2.20 (dq, *J* = 7.4, 2.0, 1H), 2.06 (dd, *J* = 14.1, 3.0, 1H), 1.82 (dd, *J* = 14.1, 3.0, 1H), 1.18 (s, 3H), 1.14 (s, 3H), 1.12 (d, *J* = 7.4, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 211.6, 200.9, 165.5, 127.6, 69.4, 58.2, 49.1, 41.1, 39.0, 34.6, 30.3, 29.4, 23.7, 14.0, 11.0. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{21}O_3^+$ $[M+H]^+$: 249.1485, found: 249.1485; for $C_{15}H_{20}NaO_3^+$ $[M+Na]^+$: 271.1305, found: 281.1306.



2.74 → 11*R*-**2.76** + 11*S*-**2.76**

80 %, *dr* 2:1 (11*R*/11*S*)

A solution of **2.74** (280 mg, 0.772 mmol, 1.0 equiv.) and $HSiEt_3$ (149 µL, 0.926 mmol, 1.2 equiv.) in THF (3.0 mL) was added to a suspension of $PdCl_2$ (6.84 mg, 38.6 µmol, 5 mol%) and PCy_3 (21.6 mg, 77.2 µmol 10 mol%) in THF/H_2O (9.0 mL, 1:2). The mixture was stirred at rt for 90 min, before it was filtered through a short plug of Al_2O_3 (eluted with EtOAc). The solvent was evaporated and the residue subjected to flash column chromatography (pentane/Et_2O 1:1) to give **2.76** (224 mg, 0.614 mmol, 80 %, *dr* 2:1 11*R*/11*S*) as a yellowish oil. For analytical purposes, **2.76** was purified by additional flash column chromatography (pentane/Et_2O 5:2) to give 11*R*-**2.76** as a colorless solid and 11*S*-**2.76** as a colorless oil.

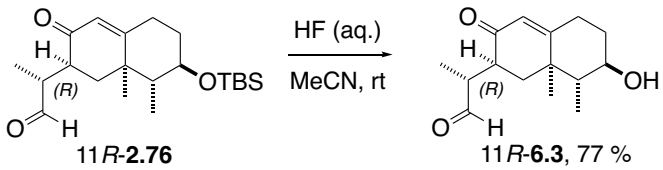
(*R*)-2-((2*S*,7*R*,8*R*,8a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)propanal (11*R*-**2.76):**

M.p. = 85.0 – 89.1°C. TLC: R_f = 0.50 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = +64.3° (c = 0.52, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2930, 2857, 1724, 1670, 1625, 1462, 1361, 1252, 1223, 1131, 1098, 1070, 1007, 955, 889, 868, 834, 774, 685 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 9.76 (s, 1H), 5.75 (d, *J* = 1.8, 1H), 3.57 (td, *J* = 10.5, 4.3, 1H), 3.02 (ddd, *J* = 14.6, 4.7, 3.5, 1H), 2.57 (qd, *J* = 7.2, 3.5, 1H), 2.41 (tdd, *J* = 14.5, 5.1, 2.0, 1H), 2.31 (ddd, *J* = 15.0, 4.5, 2.8,

1H), 2.03 (dtd, *J* = 12.3, 4.8, 2.7, 1H), 1.96 (dd, *J* = 13.0, 4.7, 1H), 1.70 (t, *J* = 13.9 Hz, 1H), 1.46 (dddd, *J* = 14.4, 12.5, 10.9, 4.5, 1H), 1.37 (dq, *J* = 10.0, 6.8, 1H), 1.17 (s, 3H), 1.15 (d, *J* = 7.2, 3H), 0.99 (d, *J* = 6.7, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 204.3, 198.2, 169.3, 124.0, 71.8, 50.6, 45.6, 44.4, 40.2, 39.6, 35.7, 31.3, 26.0 (3C), 18.2, 17.5, 11.2, 9.7, -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{21}H_{36}NaO_3Si^+$ $[M+Na]^+$: 387.2326, found: 387.2328.

(*S*)-2-((2*S*,7*R*,8*R*,8a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)propanal (11*S*-**2.76):**

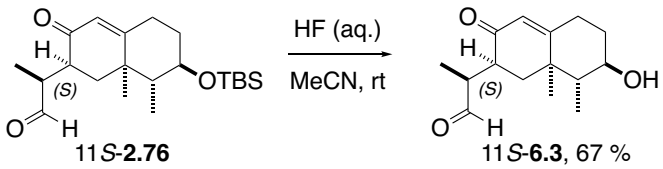
TLC: R_f = 0.61 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{23}$ = +35.8° (c = 0.71, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2930, 2857, 1724, 1672, 1626, 1462, 1361, 1252, 1132, 1098, 1070, 1006, 889, 834, 774, 690, 581 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 9.76 (s, 1H), 5.76 (d, *J* = 1.7, 1H), 3.56 (td, *J* = 10.5, 4.3, 1H), 3.07 (qd, *J* = 7.1, 4.5, 1H), 2.96 (dt, *J* = 14.5, 4.5, 1H), 2.40 (tdd, *J* = 14.6, 5.1, 1.9, 1H), 2.30 (ddd, *J* = 14.9, 4.6, 2.7, 1H), 2.03 (dtd, *J* = 12.4, 4.8, 2.7, 1H), 1.87 (dd, *J* = 13.0, 4.5, 1H), 1.54 – 1.40 (m, 2H), 1.33 (dq, *J* = 10.0, 6.7, 1H), 1.17 (s, 3H), 1.07 (d, *J* = 7.3, 3H), 0.96 (d, *J* = 6.8, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 204.3, 198.6, 169.0, 123.8, 71.8, 50.7, 44.9, 42.0, 40.0, 38.4, 35.7, 31.2, 26.0 (3C), 18.2, 17.4, 11.1, 10.1, -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{21}H_{37}O_3Si^+$ $[M+Na]^+$: 365.25065, found: 365.25057.



11*R*-**2.76** 11*R*-**6.3**, 77 %

(*R*)-2-((2*S*,7*R*,8*R*,8a*R*)-7-Hydroxy-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydro-naphthalen-2-yl)propanal (11*R*-**6.3):** To a solution of 11*R*-**2.76** (54.0 mg, 0.148 mmol, 1.0 equiv.) in MeCN (2.5 mL) was added a solution of HF (48 % in H_2O, 62 µL, 1.48 mmol, 10 equiv.). The mixture was stirred for 2.5 h, before it was quenched by addition of sat. aq. $NaHCO_3$ solution. The mixture was extracted with Et_2O (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (Et_2O) to give 11*R*-**6.3** (28.4 mg, 0.114 mmol, 77 %) as a colorless oil.

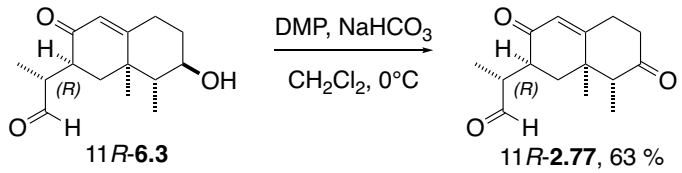
TLC: R_f = 0.25 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{25}$ = +91.8° (c = 0.64, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 1972, 2939, 2879, 1718, 1660, 1621, 1445, 1370, 1345, 1254, 1223, 1032, 961, 953, 924, 897, 871, 731, 686, 580 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 9.73 (s, 1H), 5.74 (d, *J* = 1.7, 1H), 3.59 (td, *J* = 10.7, 4.3, 1H), 3.00 (dt, *J* = 14.7, 4.2, 1H), 2.58 (qd, *J* = 7.2, 3.6, 1H), 2.43 (tdd, *J* = 14.5, 5.1, 1.9, 1H), 2.33 (ddd, *J* = 15.1, 4.7, 2.7, 1H), 2.14 (dtd, *J* = 12.3, 4.8, 2.7, 1H), 1.96 (dd, *J* = 13.0, 4.7, 1H), 1.69 (t, *J* = 13.8, 1H), 1.42 (dtd, *J* = 14.2, 11.8, 4.8, 1H), 1.31 (dq, *J* = 10.2, 6.7, 1H), 1.16 (s, 3H), 1.14 (d, *J* = 7.1, 3H), 1.06 (d, *J* = 6.7, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 204.2, 198.2, 168.9, 124.1, 71.0, 50.3, 45.5, 44.2, 40.1, 39.3, 35.1, 31.1, 17.4, 10.6, 9.7. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{23}O_3^+$ $[M+H]^+$: 251.16417, found: 251.16432.



11*S*-**2.76** 11*S*-**6.3**, 67 %

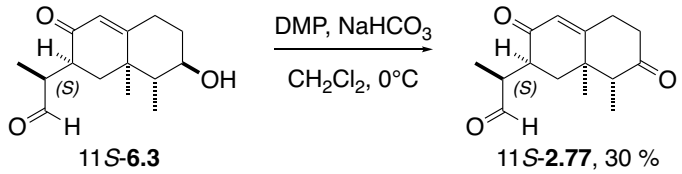
(*S*)-2-((2*S*,7*R*,8*R*,8a*R*)-7-Hydroxy-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)propanal (11*S*-**6.3):** To a solution of 11*S*-**2.76** (72.6 mg, 0.199 mmol, 1.0 equiv.) in MeCN (3.3 mL) was added a solution of HF (48 % in H_2O, 84 µL, 1.99 mmol, 10 equiv.). The mixture was stirred for 2.5 h, before it was quenched by addition of sat. aq. $NaHCO_3$ solution. The mixture was extracted with Et_2O (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (Et_2O) to give 11*S*-**6.3** (33.4 mg, 0.133 mmol, 67 %) as a colorless oil.

TLC: R_f = 0.28 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{24}$ = +50.8° (c = 0.48, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3425, 2971, 2938, 2878, 1720, 1663, 1623, 1445, 1373, 1256, 1221, 1032, 954, 923, 871, 731, 698, 582 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.75 (s, 1H), 5.78 (d, *J* = 1.8, 1H), 3.61 (td, *J* = 10.7, 4.4, 1H), 3.05 (qd, *J* = 7.2, 4.5, 1H), 2.97 (dt, *J* = 14.4, 4.6, 1H), 2.45 (tdd, *J* = 14.2, 5.1, 1.9, 1H), 2.34 (ddd, *J* = 15.0, 4.8, 2.6, 1H), 2.15 (dtd, *J* = 12.2, 4.8, 2.7, 1H), 1.89 (dd, *J* = 13.0, 4.5, 1H), 1.56 – 1.47 (m, 1H), 1.47 – 1.39 (m, 1H), 1.32 – 1.24 (m, 1H), 1.18 (s, 3H), 1.08 (d, *J* = 7.3, 3H), 1.05 (d, *J* = 6.8, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 204.2, 198.6, 168.5, 124.0, 71.1, 50.4, 44.9, 42.0, 40.0, 38.3, 35.2, 31.1, 17.3, 10.5, 10.2. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{22}NaO_3^+$ $[M+Na]^+$: 273.14612, found: 273.14558.



(*R*)-2-((2*S*,8*R*,8a*R*)-8,8a-Dimethyl-3,7-dioxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)propanal (11*R*-**2.77):** $NaHCO_3$ (230 mg, 2.74 mmol, 8.0 equiv.) and DMP (290 mg, 0.684 mmol, 2.0 equiv.) were sequentially added to a solution of 11*R*-**6.3** (85.6 mg, 0.342 mmol, 1.0 equiv.) in CH_2Cl_2 (4.3 mL) at 0°C and the mixture was stirred for 2 h. Sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ solutions were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 2:1 to Et_2O) to give 11*R*-**2.77** (53.2 mg, 0.342 mmol, 63 %) as a yellowish oil.

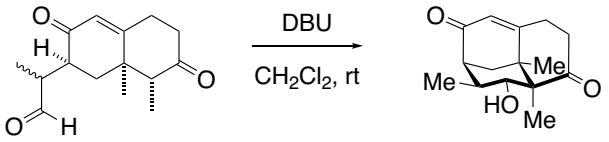
TLC: R_f = 0.34 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{24}$ = +69.0° (c = 0.72, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2974, 2943, 2724, 1712, 1666, 1624, 1445, 1366, 1345, 1254, 1222, 1181, 1074, 1008, 958, 922, 893, 865, 827, 797, 770, 727, 678, 623, 570 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 9.74 (s, 1H), 5.92 (s, 1H), 2.98 (ddd, *J* = 11.5, 7.9, 3.7, 1H), 2.81 – 2.74 (m, 2H), 2.69 (qd, *J* = 7.3, 3.6, 1H), 2.62 – 2.48 (m, 3H), 1.98 – 1.92 (m, 2H), 1.19 (d, *J* = 7.3, 3H), 1.13 (s, 3H), 1.05 (d, *J* = 6.7, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 209.7, 204.0, 197.8, 165.3, 125.4, 54.1, 45.6, 44.7, 43.6, 40.0, 39.1, 32.3, 18.4, 10.1, 7.5. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{21}O_3^+$ $[M+H]^+$: 249.14852, found: 249.14863.



(*S*)-2-((2*S*,8*R*,8a*R*)-8,8a-Dimethyl-3,7-dioxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)propanal (11*S*-**2.77):** $NaHCO_3$ (89.4 mg, 1.06 mmol, 8.0 equiv.) and DMP (113 mg, 0.266 mmol, 2.0 equiv.) were added sequentially to a solution of 11*S*-**6.3** (33.3 mg, 0.133 mmol, 1.0 equiv.) in CH_2Cl_2 (1.7 mL) at 0°C and the mixture was stirred for 1 h. Sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ solutions were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column

chromatography (pentane/Et_2O 2:1 to Et_2O) to give 11*S*-**2.77** (10.0 mg, 40 µmol, 30 %) as a colorless oil.

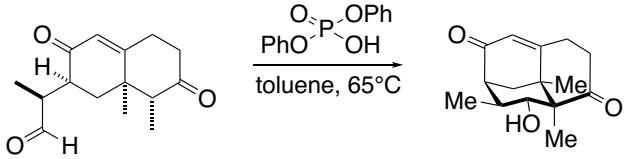
TLC: R_f = 0.33 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{24}$ = +24.0° (c = 0.50, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2971, 2920, 2851, 1713, 1669, 1625, 1446, 1375, 1345, 1254, 1221, 1180, 1074, 1051, 1014, 974, 921, 865, 798, 578 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.76 (s, 1H), 5.93 (s, 1H), 3.07 (dt, *J* = 11.8, 7.2, 1H), 2.98 (dt, *J* = 14.4, 4.5, 1H), 2.77 (dt, *J* = 10.5, 6.3, 2H), 2.60 – 2.52 (m, 2H), 2.48 (q, *J* = 6.8, 1H), 1.89 (dd, *J* = 13.0, 4.6, 1H), 1.75 (t, *J* = 13.7, 1H), 1.15 (s, 3H), 1.11 (d, *J* = 7.4, 3H), 1.03 (d, *J* = 6.8, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ = 209.4, 203.8, 198.0, 164.8, 125.0, 54.0, 44.8, 43.3, 42.4, 39.9, 38.2, 32.1, 18.0, 10.3, 7.2. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{21}O_3^+$ $[M+H]^+$: 249.14852, found: 249.14856.



11*R*-**2.77**/11*S*-**2.77** 11*S*-**2.70**, 50 %, *dr* 9:1

(1*R*,7*S*,8a*S*,9*S*,10*R*)-10-Hydroxy-1,8a,9-trimethyl-1,3,4,7,8,8a-hexahydro-1,7-ethano-naphthalene-2,6-dione (11*S*-**2.70):** To a solution of a mixture of 11*R*- and 11*S*-**2.77** (10.0 mg, 40.3 µmol, 1.0 equiv.) in CH_2Cl_2 (2.5 mL) was added DBU (18 µL, 0.121 mmol, 3.0 equiv.) and the mixture was stirred at rt for 18 h. The mixture was quenched by addition of aq. HCl (0.1 M) and diluted with Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x). The combined organic layers were washed with sat. aq. $NaHCO_3$ solution, H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (Et_2O) to give 11*S*-**2.70** (5.0 mg, 20.1 µmol, 50 %, *dr* >10:1) as a colorless solid.

or

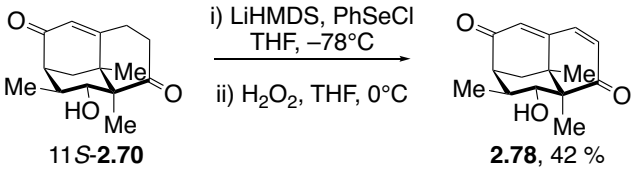


11*S*-**2.77** 11*S*-**2.70**, 50 %

To a solution of 11*S*-**2.77** (10.0 mg, 40.3 µmol, 1.0 equiv.) in toluene (1.5 mL) was added diphenyl phosphate (5.04 mg, 20.2 µmol, 0.5 equiv.) and the mixture was heated at 65°C for 4.5 h. The yellow mixture was partitioned between sat. aq $NaHCO_3$ solution and EtOAc. The

layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (Et_2O) to give 11*S*-**2.70** (5.1 mg, 21 µmol, 51 %, *dr* >10:1) as a colorless solid.

M.p. = 150.2 – 151.6°C. TLC: R_f = 0.26 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{22}$ = –89.2° (c = 0.78, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3436, 2961, 2920, 2874, 1703, 1666, 1463, 1386, 1332, 1274, 1243, 1208, 1174, 1151, 1098, 1040, 888, 750 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.13 (s, 1H), 3.82 (dd, *J* = 10.5, 5.1 Hz, 1H), 3.00 – 2.62 (m, 3H), 2.59 – 2.49 (m, 2H), 1.96 (dd, *J* = 3.1, 1.2 Hz, 2H), 1.87 – 1.70 (m, 1H), 1.44 (d, *J* = 5.7 Hz, 1H), 1.17 (s, 3H), 1.12 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 211.0, 199.2, 165.1, 127.5, 74.9, 58.9, 49.2, 41.6, 38.7, 34.7, 34.5, 30.3, 23.5, 16.1, 8.3. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{20}NaO_3^+$ $[M+Na]^+$: 271.1305, found: 271.1299.

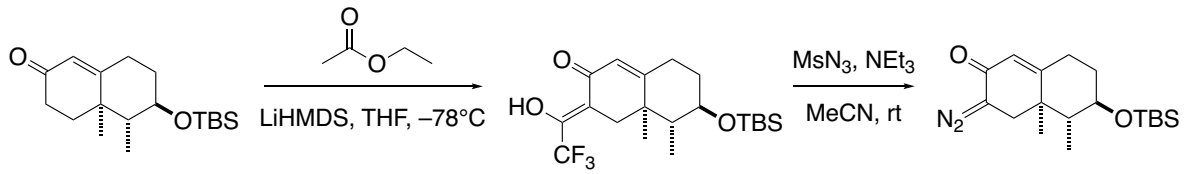


11*S*-**2.70** **2.78**, 42 %

(1*R*,7*S*,8a*S*,9*S*,10*R*)-10-Hydroxy-1,8a,9-trimethyl-1,7,8,8a-tetrahydro-1,7-ethano-naphthalene-2,6-dione (2.78): To a stirred solution of 11*S*-**2.70** (10.0 mg, 40.3 µmol, 1.0 equiv.) in THF (1.0 mL) at –78°C was added dropwise a solution of LiHMDS (1.0 M in THF, 101 µL, 101 µmol, 2.5 equiv.). After 30 min at –78°C, a solution of PhSeCl (15.4 mg, 80.6 µmol, 2.0 equiv.) in THF (0.3 mL) was added dropwise. The solution was stirred for 2 h at –78°C, before it was quenched by addition of sat. aq. NH_4Cl solution and extracted with Et_2O (3 x). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in THF (1.5 mL) and a solution of H_2O_2 (30 % in H_2O, 30 µL, 0.322 mmol, 8.0 equiv.) was added at 0°C. After stirring for 90 min the mixture was warmed up to rt and stirred for another 90 min. Sat. aq. $Na_2S_2O_3$ solution and Et_2O were added and the layers were separated. The aqueous layer was extracted with Et_2O (2 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 1:2) to give **2.78** (4.2 mg, 17.1 µmol, 42 %) as a colorless solid.

M.p. = 140.5 – 146.4°C. TLC: R_f = 0.40 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{22}$ = +258.8° (c = 0.21, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3451, 2958, 2922, 2361, 1666, 1462, 1380, 1274, 1242, 1150,

1103, 1035, 903 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.29 (dd, *J* = 10.1, 1.1 Hz, 1H), 6.10 (s, 1H), 6.04 (d, *J* = 10.1 Hz, 1H), 3.51 (d, *J* = 10.4 Hz, 1H), 2.52 (dt, *J* = 5.7, 3.2 Hz, 1H), 2.12 (dd, *J* = 14.3, 3.3 Hz, 1H), 1.97 – 1.89 (m, 1H), 1.90 (dd, *J* = 14.3, 2.8 Hz, 1H), 1.70 (s, 1H), 1.25 (s, 3H), 1.22 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 201.1, 198.5, 160.4, 143.5, 129.5, 126.1, 72.9, 55.8, 48.9, 42.9, 37.1, 33.2, 24.6, 16.6, 8.0. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{18}NaO_3^+$ $[M+Na]^+$: 269.1148, found: 269.1148.



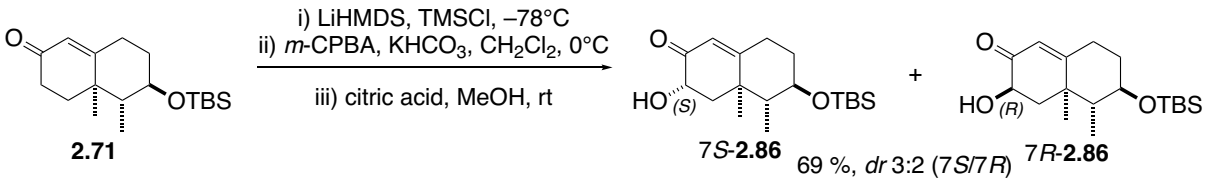
2.71 **6.4**, quant. **2.82**, 61 % over 2 steps

(4a*R*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-diazo-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.82): To a cooled (–78°C) solution of **2.71** (500 mg, 1.62 mmol, 1.0 equiv.) in THF (20 mL) was added a solution of LiHMDS (1.0 M in THF, 2.11 mL, 2.11 mmol, 1.3 equiv.) dropwise *via* syringe. The resulting yellow solution was stirred for 30 min at –78°C, before 2,2,2-trifluoroethyl trifluoroacetate (308 µL, 2.27 mmol, 1.4 equiv.) was added dropwise. The mixture was stirred for 90 min at –78°C and then quenched by addition of sat. aq. NH_4Cl solution and diluted with Et_2O. The layers were separated and the aqueous layer extracted with Et_2O (2 x). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated to give crude **6.4** (651 mg, 1.62 mmol, quant.) as a colorless oil.

Crude **6.4** (611 mg, 1.51 mmol, 1.0 equiv.) was dissolved in MeCN (4.5 mL). Et_3N (637 µL, 4.53 mmol, 3.0 equiv.) was added, followed by dropwise addition of a solution of MsN_3 (238 mg, 1.96 mmol, 1.3 equiv.) in MeCN (4.5 mL) over a period of 90 min. The yellow mixture was stirred for 3.5 h at rt, before it was diluted with Et_2O and washed with 1.0 M aq. NaOH solution. After separation, the aqueous layer was extracted with Et_2O (2 x) and the combined organics were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O/Et_3N 300:100:4) to give **2.82** (344 mg, 0.925 mmol, 61 %) as a yellow oil.

TLC: R_f = 0.41 (SiO_2, pentane/Et_2O 2:1). **Optical rotation**: $[\alpha]_D^{24}$ = +94.2° (c = 0.75, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2931, 2884, 2857, 2077, 1640, 1602, 1440, 1356, 1300, 1253, 1220, 1188, 1068, 1007, 872, 834, 775, 676 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.75 (d, *J* = 1.9 Hz,

1H), 3.52 (td, *J* = 10.5, 4.2 Hz, 1H), 2.80 (d, *J* = 14.0 Hz, 1H), 2.65 (d, *J* = 14.1 Hz, 1H), 2.47 – 2.30 (m, 2H), 2.02 – 1.93 (m, 1H), 1.52 – 1.39 (m, 2H), 1.13 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 183.9, 163.4, 124.3, 72.0, 58.6, 49.6, 40.3, 35.1, 35.0, 31.0, 26.0 (3C), 19.0, 18.2, 11.6, -3.9, -4.6. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{31}O_2N_2Si^+$ $[M+H]^+$: 335.21493, found: 335.21471; for $C_{18}H_{30}NaO_2N_2Si^+$ $[M+Na]^+$: 357.19688, found: 357.19671.



2.71 7*S*-**2.86** 69 %, *dr* 3:2 (7*S*/7*R*) 7*R*-**2.86**

To a cooled (–78°C) solution of **2.71** (2.49 g, 8.07 mmol, 1.0 equiv.) in THF (60 mL) was added a solution of LiHMDS (1.0 M in THF, 10.5 mL, 10.5 mmol, 1.3 equiv.) dropwise *via* syringe. The resulting solution was stirred for 30 min at –78°C, before TMSCl (1.34 mL, 10.5 mmol, 1.3 equiv.) was added dropwise. The mixture was stirred for 1 h at –78°C, and was then quenched by addition of sat. aq. $NaHCO_3$ solution and diluted with Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated to a colorless oil.

The crude residue was dissolved in CH_2Cl_2 (80 mL) and cooled to 0°C. $KHCO_3$ (4.04 g, 40.4 mmol, 5.0 equiv.) and *m*-CPBA (77 %, 2.35 mg, 10.5 mmol, 1.3 equiv.) were added sequentially and the mixture was stirred at 0°C for 2.5 h. Sat. aq. $Na_2S_2O_3$ solution was added and the mixture was extracted with CH_2Cl_2 (3 x). The combined organic layers were washed with H_2O (2 x), dried over Na_2SO_4, filtered and conentrated.

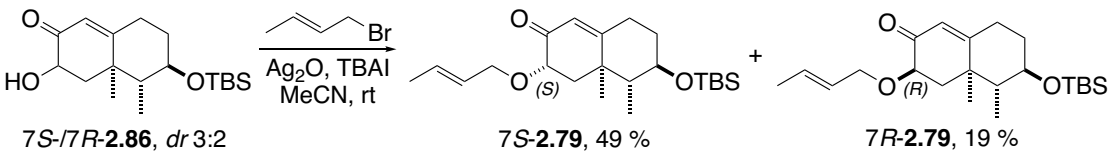
The crude residue was dissolved in MeOH (70 mL) and citric acid monohydrate (8.48 g, 40.4 mmol, 5.0 equiv.) was added. The mixture was stirred o.n., before most of the solvent was evaporated. The residue was partitioned between Et_2O and H_2O and the layers were separated. The aqueous layer was extracted with Et_2O (2 x) and the combined organic layers were dried over Na_2SO_4, filterd and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to give **2.86** (1.80 g, 5.55 mmol, 69 %, *dr* 3:2) as a yellowish solid. For analytical purposes, pure fractions of both diastereoisomers 7*S*-**2.86** and 7*R*-**2.86** were collected separately after flash column chromatography (pentane/Et_2O 2:1) to give access to both diastereoisomers with a *dr* > 20:1.

(3*S*,4a*R*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (7*S*-2.86):

TLC: R_f = 0.61 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = –130.1° (c = 0.95, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3484, 2955, 2930, 2885, 2858, 1686, 1622, 1472, 1388, 1361, 1256, 1223, 1125, 1099, 1072, 1006, 939, 888, 862, 836, 775, 727, 694, 490 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.82 (d, *J* = 1.3 Hz, 1H), 4.21 (dd, *J* = 13.8, 5.7 Hz, 1H), 3.66 (ddd, *J* = 11.0, 9.5, 5.0 Hz, 1H), 3.46 (s, 1H), 2.53 (dddd, *J* = 14.2, 12.6, 4.9, 1.5 Hz, 1H), 2.46 (dd, *J* = 13.7, 5.8 Hz, 1H), 2.23 (ddd, *J* = 12.6, 4.6, 2.7 Hz, 1H), 2.16 (dtd, *J* = 12.7, 4.9, 2.7 Hz, 1H), 1.80 (dq, *J* = 9.5, 6.6 Hz, 1H), 1.49 (t, *J* = 13.8 Hz, 1H), 1.47 – 1.38 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.09 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 199.8, 172.8, 119.5, 72.5, 68.7, 45.9, 41.3, 40.0, 38.3, 31.2, 26.0 (3C), 22.7, 18.2, 12.9, -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{33}O_3Si^+$ $[M+H]^+$: 325.21935, found: 325.22011; for $C_{18}H_{32}NaO_3Si^+$ $[M+Na]^+$: 347.20129, found: 347.20205.

(3*R*,4a*R*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (7*R*-2.86):

TLC: R_f = 0.49 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = +77.0° (c = 0.94, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3432, 2952, 2931, 2859, 1676, 1611, 1462, 1388, 1318, 1258, 1227, 1119, 1102, 1074, 1007, 890, 872, 837, 772, 730, 696, 673 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.81 (d, *J* = 1.7 Hz, 1H), 4.24 (dd, *J* = 13.7, 5.7 Hz, 1H), 3.57 (td, *J* = 10.5, 4.4 Hz, 1H), 3.51 (s, 1H), 2.46 – 2.37 (m, 2H), 2.34 (ddd, *J* = 14.8, 4.7, 2.7 Hz, 1H), 2.04 (dtd, *J* = 12.4, 4.8, 2.8 Hz, 1H), 1.58 (t, *J* = 13.2 Hz, 1H), 1.46 (dddd, *J* = 14.2, 12.5, 10.9, 4.7 Hz, 1H), 1.37 (dq, *J* = 10.0, 6.7 Hz, 1H), 1.22 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 199.7, 171.2, 120.8, 71.3, 69.2, 50.8, 44.4, 41.3, 35.8, 31.5, 26.0 (3C), 18.2, 18.1, 10.9, -3.9, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{33}O_3Si^+$ $[M+H]^+$: 325.21935, found: 325.21874; for $C_{18}H_{32}NaO_3Si^+$ $[M+Na]^+$: 347.20129, found: 347.20068.



7*S*-/7*R*-**2.86**, *dr* 3:2 7*S*-**2.79**, 49 % 7*R*-**2.79**, 19 %

To a stirred solution of a mixture of 7*S*- and 7*R*-**2.86** (50 mg, 0.154 mmol, 1.0 equiv., *dr* 3:2) and TBAI (28 mg, 77 µmol, 0.5 equiv.) in CH_2Cl_2 (3.0 mL) was added Ag_2O (178 mg, 0.77 mmol, 5.0 equiv.) and crotyl bromide (93 µL, 0.77 mmol, 5.0 equiv.). The reaction mixture was stirred at rt o.n. and then filtered through a short plug of celite. The solvent was removed by evaporation and the residue subjected to flash column chromatography (pentane/Et_2O 5:1) to give 7*S*-**2.79** (28.4 mg, 75 µmol, 49 %) and 7*R*-**2.79** (10.9 mg, 29 µmol, 19 %) both as colorless oils.

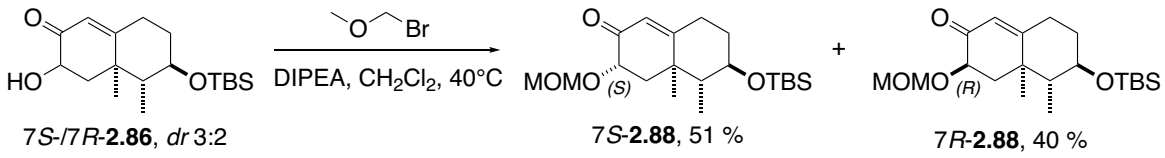
(3*S*,4a*R*,5*R*,6*R*)-3-(((*E*)-But-2-en-1-yl)oxy)-6-((*tert*-butyldimethylsilyl)oxy)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (7*S*-2.79):

TLC: R_f = 0.54 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{23}$ = –37.6° (c = 1.42, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2929, 2857, 1731, 1674, 1624, 1463, 1387, 1360, 1283, 1256, 1221, 1128, 1098, 1074, 1040, 1006, 966, 941, 887, 834, 774, 667, 509 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.74 (d, *J* = 1.4 Hz, 1H), 5.75 – 5.68 (m, 1H), 5.59 – 5.53 (m, 1H), 4.14 (ddt, *J* = 11.8, 5.8, 1.3 Hz, 1H), 3.94 (ddp, *J* = 9.9, 6.4, 1.1 Hz, 1H), 3.82 (t, *J* = 6.3 Hz, 1H), 3.61 (ddd, *J* = 11.0, 9.7, 4.7 Hz, 1H), 2.48 (tdd, *J* = 14.1, 5.0, 1.6 Hz, 1H), 2.26 – 2.21 (m, 1H), 2.09 (dtd, *J* = 12.5, 4.9, 2.6 Hz, 1H), 2.04 – 1.96 (m, 2H), 1.70 (dq, *J* = 6.4, 1.3 Hz, 3H), 1.50 (dq, *J* = 9.6, 6.7 Hz, 1H), 1.42 (dddd, *J* = 14.3, 12.5, 11.0, 4.6 Hz, 1H), 1.17 (s, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 197.4, 170.0, 129.7, 127.5, 121.8, 75.6, 72.1, 71.0, 48.8, 40.5, 40.3, 37.2, 31.4, 26.0 (3C), 21.7, 18.2, 17.9, 11.9, -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{22}H_{39}O_3Si^+$ $[M+H]^+$: 379.2663, found: 379.2665; for $C_{22}H_{38}NaO_3Si^+$ $[M+Na]^+$: 401.2482, found: 401.2487.

(3*R*,4a*R*,5*R*,6*R*)-3-(((*E*)-But-2-en-1-yl)oxy)-6-((*tert*-butyldimethylsilyl)oxy)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (7*R*-2.79):

TLC: R_f = 0.31 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{24}$ = +52.9° (c = 0.54, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2929, 2857, 1693, 1462, 1255, 1128, 1103, 1077, 889, 835, 775 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.79 – 5.71 (m, 1H), 5.69 (d, *J* = 1.8 Hz, 1H), 5.64 (dtq, *J* = 15.7, 6.4, 1.6 Hz, 1H), 4.36 (ddt, *J* = 11.5, 6.1, 1.2 Hz, 1H), 4.04 (ddt, *J* = 11.5, 6.5, 1.1 Hz, 1H), 3.99 (dd, *J* = 13.8, 5.2 Hz, 1H), 3.54 (td, *J* = 10.4, 4.4 Hz, 1H), 2.41 – 2.26 (m, 2H), 2.24 (dd, *J* = 12.7, 5.1 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.72 – 1.67 (m, 4H), 1.44 (dddd, *J* = 14.2, 12.5, 11.0, 4.8 Hz, 1H), 1.39 – 1.32 (m, 1H), 1.18 (s, 3H), 0.98 (dd, *J* = 6.8, 1.2 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 198.8, 168.1, 130.2, 127.6, 122.8, 75.1, 71.7, 71.5, 50.7, 43.2, 41.4, 35.9, 31.0, 26.0 (3C), 18.2, 18.1, 17.9, 11.0, -3.9, -4.6.

HRMS (ESI) Exact mass calculated for $C_{22}H_{39}O_3Si^+$ $[M+H]^+$: 379.2663, found: 379.2665; for $C_{22}H_{38}NaO_3Si^+$ $[M+Na]^+$: 401.2482, found: 401.2487.



7*S*-/7*R*-**2.86**, *dr* 3:2 — 7*S*-**2.88**, 51 % — 7*R*-**2.88**, 40 %

To a mixture of 7*S*- and 7*R*-**2.86** (39.5 mg, 0.122 mmol, 1.0 equiv., *dr* 3:2) and DIPEA (81 µL, 0.488 mmol, 4.0 equiv.) in CH_2Cl_2 (2.0 mL) was added MOMBr (20 µL, 0.244 mmol, 2.0 equiv.). The mixture was allowed to stir at 40°C o.n., before additional MOMBr (10 µL, 0.122 mmol, 1.0 equiv.) was added. After stirring for 2 h at 40°C, the mixture was diluted with CH_2Cl_2 and sat. aq. $NaHCO_3$ solution was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organics were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 4:1) to give 7*S*-**2.88** (23.0 mg, 62 µmol, 51 %) and 7*R*-**2.88** (17.9 mg, 49 µmol, 40 %) both as colorless oils.

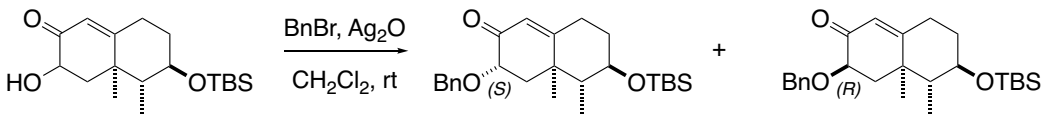
(3*S*,4a*R*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-(methoxymethoxy)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (7*S*-**2.88):**

TLC: R_f = 0.72 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = –98.1° (c = 0.63, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2952, 2929, 2886, 2857, 1692, 1625, 1472, 1387, 1361, 1257, 1213, 1130, 1097, 1076, 1038, 1007, 940, 918, 887, 835, 774, 669 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.75 (d, *J* = 1.4 Hz, 1H), 4.80 (d, *J* = 6.7 Hz, 1H), 4.71 (d, *J* = 6.7 Hz, 1H), 4.15 (dd, *J* = 9.7, 4.8 Hz, 1H), 3.62 (ddd, *J* = 10.9, 9.7, 4.8 Hz, 1H), 3.39 (s, 3H), 2.54 – 2.43 (m, 1H), 2.24 (ddd, *J* = 13.4, 4.6, 2.7 Hz, 1H), 2.16 – 2.07 (m, 2H), 1.92 (dd, *J* = 14.1, 9.7 Hz, 1H), 1.65 – 1.58 (m, 1H), 1.48 – 1.36 (m, 1H), 1.16 (s, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 197.1, 170.3, 121.7, 96.0, 73.0, 72.1, 55.8, 48.0, 40.6, 40.1, 37.5, 31.3, 26.0 (3C), 21.9, 18.2, 12.1, -3.9, -4.6. **HRMS** (ESI) Exact mass calculated for $C_{20}H_{36}NaO_4Si^+$ $[M+Na]^+$: 391.22751, found: 391.22805.

(3*R*,4a*R*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-(methoxymethoxy)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (7*R*-**2.88):**

TLC: R_f = 0.54 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{23}$ = +96.8° (c = 0.56, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2929, 2857, 1690, 1623, 1472, 1463, 1387, 1361, 1252, 1215, 1143, 1126, 1100, 1074, 1035, 1005, 888, 833, 773, 725, 693, 667 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.71 (d, *J* = 1.6 Hz, 1H), 4.89 (d, *J* = 6.8 Hz, 1H), 4.79 (d, *J* = 6.8 Hz, 1H), 4.28 (dd, *J* = 13.8,

5.3 Hz, 1H), 3.55 (td, *J* = 10.5, 4.5 Hz, 1H), 3.42 (s, 3H), 2.43 – 2.30 (m, 2H), 2.26 (dd, *J* = 12.7, 5.4 Hz, 1H), 2.03 (dtd, *J* = 12.4, 4.8, 2.7 Hz, 1H), 1.75 (t, *J* = 13.2 Hz, 1H), 1.50 – 1.41 (m, 1H), 1.41 – 1.33 (m, 1H), 1.21 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 197.8, 168.6, 122.7, 96.4, 73.0, 71.5, 55.8, 50.7, 43.3, 41.3, 35.8, 31.1, 26.0 (3C), 18.2, 18.2, 11.0, -3.9, -4.6. **HRMS** (ESI) Exact mass calculated for $C_{20}H_{37}O_4Si^+$ $[M+H]^+$: 369.24556, found: 369.24620; for $C_{20}H_{36}NaO_4Si^+$ $[M+Na]^+$: 391.22751, found: 391.22802.



7*S*-/7*R*-**2.86**, *dr* 3:2 7*S*-**2.90**, 51 % 7*R*-**2.90**, 36 %

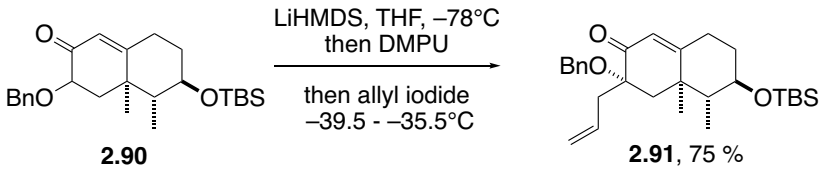
To a mixture of 7*S*- and 7*R*-**2.86** (425 mg, 1.31 mmol, 1.0 equiv., *dr* 3:2) in CH_2Cl_2 (18.0 mL) were added Ag_2O (911 mg, 3.93 mmol, 3.0 equiv.) and BnBr (470 µL, 3.93 mmol, 3.0 equiv.). The mixture was stirred at rt for 2.5 h, before it was filtered through Celite (eluted with CH_2Cl_2). The solvent was evaporated and the residue was purified by flash column chromatography (pentane/Et_2O 4:1) to give 7*S*-**2.90** (277 mg, 0.668 mmol, 51 %) as colorless oil and 7*R*-**2.90** (194 mg, 0.468 mmol, 36 %) as colorless solid.

(3*S*,4a*R*,5*R*,6*R*)-3-(Benzyloxy)-6-((*tert*-butyldimethylsilyl)oxy)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (7*S*-**2.90):**

TLC: R_f = 0.65 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{27}$ = –59.7° (c = 0.32, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2928, 2856, 1674, 1624, 1472, 1463, 1251, 1130, 1098, 1075, 888, 834, 774, 734, 696, 667 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.37 – 7.27 (m, 5H), 5.77 (s, 1H), 4.78 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 3.85 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.60 (td, *J* = 10.4, 4.6 Hz, 1H), 2.48 (tdd, *J* = 14.2, 4.9, 1.3 Hz, 1H), 2.25 (ddd, *J* = 13.7, 4.5, 2.7 Hz, 1H), 2.15 – 2.05 (m, 2H), 1.97 (dd, *J* = 14.4, 4.5 Hz, 1H), 1.49 – 1.36 (m, 2H), 1.21 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.2, 170.3, 138.4, 128.5 (2C), 127.7 (2C), 127.7, 121.8, 76.1, 72.2, 72.0, 49.1, 41.0, 40.2, 37.1, 31.5, 26.0 (3C), 21.7, 18.2, 11.8, -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{25}H_{39}O_3Si^+$ $[M+H]^+$: 415.26630, found: 415.26630.

(3*R*,4a*R*,5*R*,6*R*)-3-(Benzyloxy)-6-((*tert*-butyldimethylsilyl)oxy)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (7*R*-**2.90):**

M.p. = 51.0 – 56.1°C. TLC: R_f = 0.48 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{27}$ = +91.7° (c = 0.29, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2928, 2856, 1693, 1623, 1472, 1462, 1253, 1217, 1128, 1103, 1080, 1062, 889, 834, 774, 696, 679 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.44 – 7.39 (m, 2H), 7.39 – 7.32 (m, 2H), 7.31 – 7.27 (m, 1H), 5.71 (d, *J* = 1.4 Hz, 1H), 5.03 (d, *J* = 11.8 Hz, 1H), 4.66 (d, *J* = 11.8 Hz, 1H), 4.04 (dd, *J* = 13.7, 5.2 Hz, 1H), 3.54 (td, *J* = 10.5, 4.4 Hz, 1H), 2.43 – 2.27 (m, 2H), 2.24 (dd, *J* = 12.7, 5.2 Hz, 1H), 2.02 (dtd, *J* = 12.3, 4.7, 2.8 Hz, 1H), 1.77 (t, *J* = 13.2 Hz, 1H), 1.45 (dddd, *J* = 13.9, 12.5, 11.1, 5.0 Hz, 1H), 1.39 – 1.32 (m, 1H), 1.13 (s, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 198.8, 168.3, 138.4, 128.5 (2C), 128.1 (2C), 127.9, 122.8, 75.4, 72.9, 71.5, 50.7, 43.2, 41.4, 35.9, 31.0, 26.0 (3C), 18.2, 18.1, 11.0, -3.9, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{25}H_{39}O_3Si^+$ $[M+H]^+$: 415.26630, found: 415.26630.

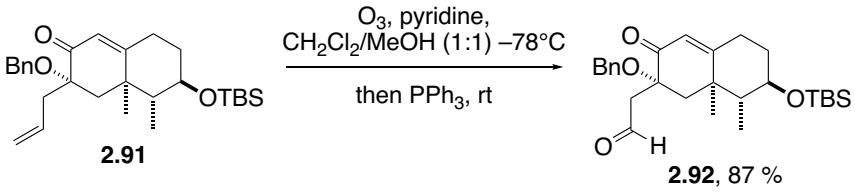


2.90 **2.91**, 75 %

(3*S*,4a*R*,5*R*,6*R*)-3-Allyl-3-(benzyloxy)-6-((*tert*-butyldimethylsilyl)oxy)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.91): To a cooled (–78°C) solution of **2.90** (1.50 g, 3.62 mmol, 1.0 equiv.) in THF (38 mL) was added dropwise a solution of LiHMDS (1.0 M in THF, 8.70 mL, 8.70 mmol, 2.4 equiv.). The mixture was stirred for 60 min, before DMPU (1.75 mL, 14.5 mmol, 4.0 equiv.) was added and stirring was continued for further 30 min at –78°C. Then allyl iodide (2.64 mL, 29.0 mmol, 8.0 equiv.), freshly filtered through a plug of K_2CO_3, was added dropwise. The mixture was immediately warmed up to –40°C and stirred for 16 h between –35.5°C and –39.5°C. The mixture was quenched by addition of sat. aq. NH_4Cl solution and extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude mixture was subjected to flash column chromatography (pentane/Et_2O 10:1) to give **2.91** (1.24 g, 2.73 mmol, 75 %) as a colorless oil.

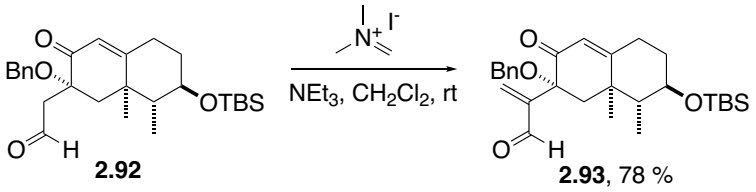
TLC: R_f = 0.87 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{26}$ = –10.8° (c = 1.06, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2929, 2857, 1671, 1628, 1498, 1462, 1386, 1257, 1074, 888, 835, 774, 733, 697 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.32 – 7.25 (m, 2H), 7.26 – 7.19 (m, 3H), 5.80 (d, *J* = 1.4 Hz, 1H), 5.84 – 5.71 (m, 1H), 5.17 – 5.11 (m, 1H), 5.11 (s, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 4.19 (d, *J* = 11.3 Hz, 1H), 3.56 (td, *J* = 10.5, 4.5 Hz, 1H), 2.85 (dd, *J* = 14.7, 7.2 Hz, 1H), 2.45 (td, *J* = 14.0, 4.6 Hz, 1H), 2.40 – 2.31 (m, 2H), 2.28 (ddd, *J* = 14.4, 4.4, 2.6 Hz, 1H), 2.10

– 2.01 (m, 1H), 1.60 (d, *J* = 14.9 Hz, 1H), 1.49 – 1.37 (m, 1H), 1.26 (s, 3H), 1.31 – 1.23 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 196.5, 170.4, 138.7, 133.3, 128.3 (2C), 127.5 (2C), 127.4, 121.9, 118.7, 77.5, 71.6, 65.7, 51.9, 46.7, 39.7, 36.4, 36.2, 31.7, 26.0 (3C), 21.1, 18.2, 11.2, -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{28}H_{43}O_3Si^+$ $[M+H]^+$: 455.29760, found: 455.29783.



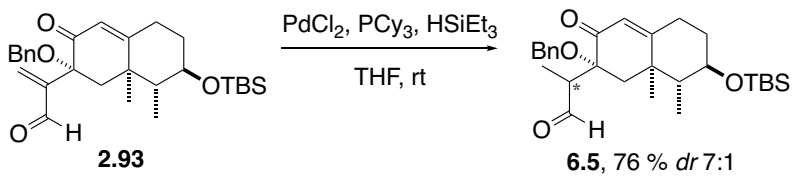
2-((2*R*,7*R*,8*R*,8a*R*)-2-(Benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)acetaldehyde (2.92): A solution of **2.91** (430 mg, 0.946 mmol, 1.0 equiv.), pyridine (305 µL, 3.78 mmol, 4.0 equiv.) and Sudan III (spatula tip) in CH_2Cl_2/MeOH (26 mL, 1:1) was cooled to –78°C and O_3 was bubbled through the solution until the red color disappeared (7 min). The reaction mixture was sequentially purged with O_2 and N_2, before PPh_3 (496 mg, 1.89 mmol, 2.0 equiv.) was added and the mixture was allowed to warm up to rt. After stirring for 2 h, the solvent was removed by evaporation and the residue was subjected to flash column chromatography (pentane/Et_2O 3:1) to give **2.92** (376 mg, 0.946 mmol, 87 %) as a colorless oil.

TLC: R_f = 0.31 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{28}$ = –19.0° (c = 0.30, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2951, 2857, 1723, 1673, 1626, 1473, 1387, 1251, 1127, 1100, 1071, 888, 836, 775, 734, 697. cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 9.79 (t, *J* = 2.4 Hz, 1H), 7.34 – 7.19 (m, 5H), 5.85 (d, *J* = 1.5 Hz, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.25 (d, *J* = 11.2 Hz, 1H), 3.57 (td, *J* = 10.5, 4.5 Hz, 1H), 2.96 (dd, *J* = 15.8, 2.5 Hz, 1H), 2.86 (dd, *J* = 15.8, 2.5 Hz, 1H), 2.51 – 2.43 (m, 1H), 2.43 (d, *J* = 14.4 Hz, 1H), 2.31 (ddd, *J* = 14.3, 4.4, 2.5 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.84 (d, *J* = 14.8 Hz, 1H), 1.46 (dddd, *J* = 15.0, 12.4, 10.9, 4.5 Hz, 1H), 1.35 – 1.24 (m, 1H), 1.28 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 200.9, 194.9, 171.2, 137.9, 128.5 (2C), 127.7, 127.6 (2C), 121.2, 77.5, 71.4, 66.2, 51.8, 47.4, 45.9, 40.0, 36.3, 31.8, 25.9 (3C), 21.2, 18.1, 11.2, -3.9, -4.6. **HRMS** (ESI) Exact mass calculated for $C_{27}H_{41}O_4Si^+$ $[M+H]^+$: 457.27686, found: 457.27718.



2-((2*R*,7*R*,8*R*,8a*R*)-2-(Benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)acrylaldehyde (2.93): Eschenmoser's salt (16.5 mg, 87.5 µmol, 5.0 equiv.) was added to a solution of **2.92** (8.00 mg, 17.5 µmol, 1.0 equiv.) and Et_3N (25 µL, 175 µmol, 10 equiv.) in CH_2Cl_2 (1.0 mL) at rt. The mixture was stirred for 18.5 h and then quenched by addition of sat. aq. $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 3:1) to give **2.93** (6.4 mg, 13.7 µmol, 78 %) as a colorless solid.

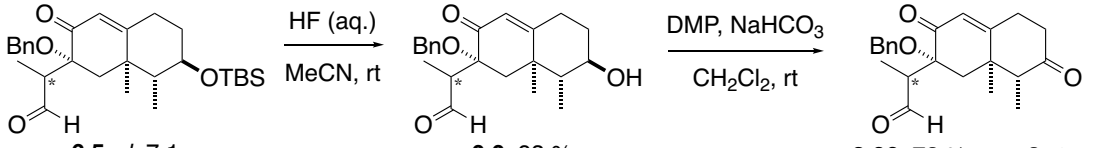
M.p. = 129.1 – 132.2°C. TLC: R_f = 0.29 (SiO_2, pentane/Et_2O 3:1), 0.63 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{28}$ = –13.5° (c = 0.42, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2928, 2856, 1700, 1671, 1627, 1462, 1293, 1251, 1116, 1099, 1069, 888, 834, 774, 733, 699, 683 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 9.60 (s, 1H), 7.34 – 7.25 (m, 5H), 6.55 (s, 1H), 6.26 (s, 1H), 5.88 (d, *J* = 1.5 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.15 (d, *J* = 12.0 Hz, 1H), 3.56 (td, *J* = 10.5, 4.4 Hz, 1H), 2.51 – 2.43 (m, 1H), 2.32 (ddd, *J* = 14.5, 4.5, 2.7 Hz, 1H), 2.18 (d, *J* = 14.5 Hz, 1H), 2.08 (d, *J* = 14.7 Hz, 1H), 2.06 – 2.02 (m, 1H), 1.56 – 1.47 (m, 1H), 1.38 (dq, *J* = 9.9, 6.7 Hz, 1H), 1.33 (s, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 193.2, 193.1, 170.6, 149.9, 138.1, 135.4, 128.4 (2C), 127.4, 127.0 (2C), 122.0, 80.2, 71.4, 66.4, 51.2, 48.3, 39.7, 36.0, 31.7, 25.8 (3C), 21.7, 18.0, 11.1, -4.0, -4.7. **HRMS** (ESI) Exact mass calculated for $C_{28}H_{40}NaO_4Si^+$ $[M+Na]^+$: 491.25881, found: 491.25899.



2-((2*R*,7*R*,8*R*,8a*R*)-2-(Benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)propanal (6.5): A solution of **2.93** (19.1 mg, 40.8 µmol, 1.0 equiv.) and Et_3SiH (33 µL, 204 µmol, 5.0 equiv.) in THF (0.5 mL) was added to a suspension of $PdCl_2$ (0.36 mg, 5 mol%) and PCy_3 (1.14 mg, 10 mol%) in H_2O (0.5 mL).

The mixture was stirred at rt and additional Et_3SiH (33 µL, 204 µmol, 5.0 equiv.) was added after 1 and 2 h. After in total 3 h at rt, the mixture was filtered through a short pad of Al_2O_3 (eluted with Et_2O) and the solvent was evaporated. The crude residue was subjected to flash column chromatography (pentane/Et_2O 5:1) to give **6.5** (14.5 mg, 30.8 µmol, 76 %, *dr* 7:1).

TLC: R_f = 0.58 (SiO_2, pentane/Et_2O 3:1, major diastereoisomer) and 0.65 (SiO_2, pentane/Et_2O 3:1, minor diastereoisomer). **FTIR** (neat): $\tilde{\nu}$ = 2952, 2929, 2856, 1723, 1669, 1628, 1462, 1250, 1099, 1072, 888, 835, 774, 733, 697 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 9.60 (s, 1H), 7.35 – 7.19 (m, 5H), 5.90 (d, *J* = 1.5 Hz, 1H), 4.36 (d, *J* = 11.2 Hz, 1H), 4.19 (d, *J* = 11.3 Hz, 1H), 3.71 (q, *J* = 7.3 Hz, 1H), 3.56 (td, *J* = 10.4, 4.5 Hz, 1H), 2.47 (tdd, *J* = 14.5, 5.1, 1.6 Hz, 1H), 2.32 (ddd, *J* = 14.4, 4.6, 2.7 Hz, 1H), 2.26 (d, *J* = 14.6 Hz, 1H), 2.06 (dtd, *J* = 12.4, 4.8, 2.6 Hz, 1H), 1.50 (d, *J* = 14.6 Hz, 1H), 1.46 (s, 1H), 1.29 (dt, *J* = 9.9, 6.7 Hz, 1H), 1.25 (s, 3H), 1.16 (d, *J* = 7.3 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, Et_3SiOH), 0.95 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.60 (q, *J* = 8.0 Hz, Et_3SiOH), 0.06 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 202.7, 195.3, 171.1, 138.0, 128.4 (2C), 127.6, 127.5 (2C), 121.9, 78.2, 71.5, 65.5, 51.8, 46.1, 43.0, 39.7, 36.2, 31.8, 25.9 (3C), 21.6, 18.1, 11.2, 6.8, 6.7 (Et_3SiOH), 6.0 (Et_3SiOH), -3.8, -4.6. **HRMS** (ESI) Exact mass calculated for $C_{28}H_{42}NaO_4Si^+$ $[M+Na]^+$: 493.27446, found: 493.27455.



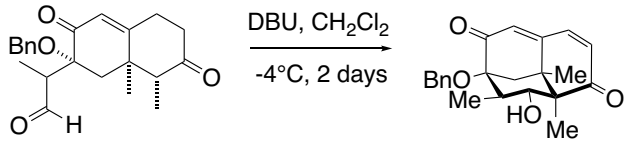
6.5, *dr* 7:1 — **6.6**, 93 % — **2.96**, 72 % over 2 steps, *dr* 10:1 (after separation)

2-((2*R*,8*R*,8a*R*)-2-(Benzyloxy)-8,8a-dimethyl-3,7-dioxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)propanal (2.96): To a solution of **6.5** (16.2 mg, 34.5 µmol, 1.0 equiv.) in MeCN (1.5 mL) was added a solution of HF (48 % in H_2O, 14.5 µL, 345 µmol, 10 equiv.) and the mixture was allowed to stir for 4 h, before it was quenched by addition of sat. aq. $NaHCO_3$ solution. The mixture was extracted with Et_2O (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 1:2) to give the alcohol **6.6** (11.4 mg, 32.0 µmol, 93 %, *dr* 7:1) as a colorless oil.

$NaHCO_3$ (21.5 mg, 256 µmol, 8.0 equiv.) and DMP (27.1 mg, 64 µmol, 2.0 equiv.) were added sequentially to a solution of **6.6** (11.4 mg, 32.0 mmol, 1.0 equiv.) in CH_2Cl_2 (1.2 mL) at rt and the mixture was stirred for 50 min at this temperature. The mixture was diluted with CH_2Cl_2

and sat. aq. $Na_2S_2O_3$ solution was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 1:1) to give **2.96** (8.8 mg, 24.8 µmol, 72 %, *dr* 10:1) as a colorless solid.

TLC: R_f = 0.23 (SiO_2, pentane/Et_2O 1:1). **FTIR** (neat): $\tilde{\nu}$ = 2977, 2943, 1717, 1670, 1498, 1455, 1387, 1276, 1241, 1179, 1053, 883, 739, 699 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 9.66 (s, 1H), 7.33 – 7.27 (m, 3H), 7.24 – 7.19 (m, 2H), 6.05 (d, *J* = 1.7 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 4.17 (d, *J* = 11.2 Hz, 1H), 3.75 (q, *J* = 7.4 Hz, 1H), 2.84 (dtd, *J* = 15.1, 10.6, 10.1, 1.9 Hz, 1H), 2.74 (dt, *J* = 15.1, 4.9 Hz, 1H), 2.59 – 2.52 (m, 2H), 2.43 (q, *J* = 6.7 Hz, 1H), 2.21 (d, *J* = 14.5 Hz, 1H), 1.84 (d, *J* = 14.6 Hz, 1H), 1.21 – 1.19 (m, 6H), 1.03 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 209.1, 202.6, 195.0, 166.4, 137.6, 128.5 (2C), 127.8, 127.5 (2C), 123.0, 78.0, 65.7, 55.3, 45.8, 42.6, 41.9, 40.3, 32.7, 22.3, 7.4, 7.0. **HRMS** (ESI) Exact mass calculated for $C_{22}H_{26}NaO_4^+$ $[M+Na]^+$: 377.17233, found: 377.17239.

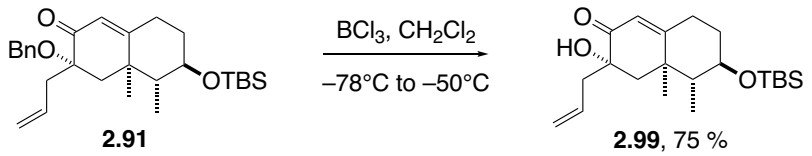


2.96 **2.97**, 25 %, *dr* >10:1

(1*R*,7*R*,8a*S*,9*R*,10*R*)-7-(Benzyloxy)-10-hydroxy-1,8a,9-trimethyl-1,7,8,8a-tetrahydro-1,7-ethanonaphthalene-2,6-dione (2.97): A solution of DBU (2.5 µL, 16.9 µmol, 3.0 equiv.) in CH_2Cl_2 (0.2 mL) was added to **2.96** (2.0 mg, 5.6 µmol, 1.0 equiv.) in CH_2Cl_2 (0.1 mL) and the mixture was stirred under an O_2 atmosphere at –4°C for 2 d. Sat. aq. NH_4Cl solution and CH_2Cl_2 were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC (Et_2O) to give **2.97** (0.4 mg, 1.1 µmol, 20 %, *dr* > 10:1) as a colorless solid.

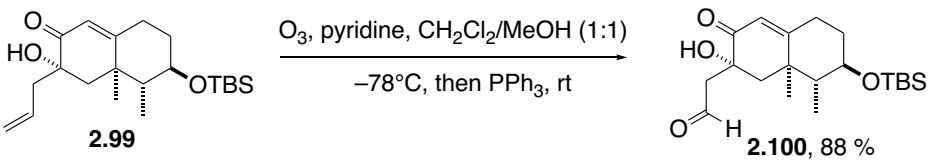
TLC: R_f = 0.58 (SiO_2, Et_2O). **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.45 (s, 2H), 7.37 – 7.33 (m, 2H), 7.29 (s, 2H), 6.10 (d, *J* = 1.0 Hz, 1H), 6.07 (d, *J* = 10.1 Hz, 1H), 4.56 (d, *J* = 10.8 Hz, 1H), 4.42 (d, *J* = 10.8 Hz, 1H), 3.54 (dd, *J* = 10.4, 3.7 Hz, 1H), 2.32 (d, *J* = 13.5 Hz, 1H), 2.34 – 2.27 (m, 1H), 2.11 (d, *J* = 13.4 Hz, 1H), 2.00 (dq, *J* = 10.3, 6.7 Hz, 1H), 1.29 (s, 3H), 1.29 (s, 3H), 1.06 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 199.6, 194.9, 158.6, 141.3, 137.6, 128.6, 127.3 (2C), 126.5, 126.4 (2C), 124.8, 80.3, 72.7, 64.7, 54.4, 43.8, 42.5, 35.9, 23.6,

11.2, 6.9. **HRMS** (ESI) Exact mass calculated for $C_{22}H_{24}NaO_4^+$ [M+Na]$^+$: 375.15668, found: 375.15682.



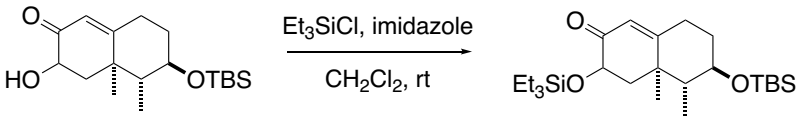
(3*S*,4a*R*,5*R*,6*R*)-3-Allyl-6-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.99): To a stirred solution of **2.91** (50 mg, 110 µmol, 1.0 equiv.) in CH_2Cl_2 (2.5 mL) at –78°C was added dropwise a solution of BCl_3 (1.0 M in CH_2Cl_2, 440 µL, 440 µmol, 4.0 equiv.) and the mixture was stirred for 20 min at this temperature, before it was allowed to warm up to –50°C and stirred for an additional 1 h. The mixture was quenched by slowly addition (crucial) of an aqueous NaOH solution (1.0 M) and then warmed up to rt. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 3:1) to give **2.99** (30.0 mg, 82.3 µmol, 75 %) as a colorless solid.

M.p. = 132.4 – 133.8°C. TLC: R_f = 0.10 (SiO_2, pentane/Et_2O 5:1). **Optical rotation**: $[\alpha]_D^{24}$ = +28.2° (c = 0.80, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3394, 2953, 2855, 1661, 1619, 1463, 1359, 1250, 1124, 1101, 1073, 1000, 918, 891, 834, 774, 579 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.81 (d, *J* = 1.8 Hz, 1H), 5.86 – 5.76 (m, 1H), 5.16 (ddd, *J* = 10.1, 2.0, 1.0 Hz, 1H), 5.11 (dq, *J* = 17.0, 1.5 Hz, 1H), 3.59 (ddd, *J* = 11.0, 9.8, 4.6 Hz, 1H), 2.73 (s, 1H), 2.55 – 2.43 (m, 2H), 2.39 (ddt, *J* = 13.9, 7.7, 1.1 Hz, 1H), 2.30 (ddd, *J* = 14.2, 4.4, 2.8 Hz, 1H), 2.08 (ddd, *J* = 12.9, 4.9, 2.9 Hz, 1H), 2.04 (d, *J* = 14.9 Hz, 1H), 1.88 (d, *J* = 14.8 Hz, 1H), 1.57 – 1.51 (m, 1H), 1.50 – 1.40 (m, 1H), 1.18 (s, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 199.9, 170.8, 132.7, 121.0, 119.7, 73.6, 72.1, 48.9, 44.6, 44.4, 40.2, 36.5, 31.5, 26.0 (3C), 22.8, 18.2, 12.0, -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{21}H_{36}NaO_3Si^+$ [M+Na]$^+$: 387.23259, found: 387.23238.



2-((2*R*,7*R*,8*R*,8a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)acetaldehyde (2.100): A solution of **2.99** (30 mg, 82.3 µmol, 1.0 equiv.), pyridine (26.5 µL, 329 µmol, 4.0 equiv.) and Sudan III (spatula tip) in CH_2Cl_2/MeOH (3.0 mL, 1:1) was cooled to –78°C and O_3 was bubbled through the solution until the red color disappeared (2 min). The reaction mixture was purged with O_2 and N_2. PPh_3 (43.2 mg, 165 µmol, 2.0 equiv.) was added and the mixture was allowed to warm up to rt. After stirring for 90 min, the solvent was removed by evaporation and the residue was purified by flash column chromatography (pentane/Et_2O 1:1) to give **2.100** (26.6 mg, 72.6 µmol, 88 %) as a colorless solid.

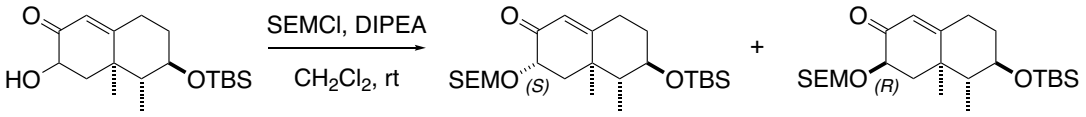
M.p. = 113.3 – 117.6°C. TLC: R_f = 0.27 (SiO_2, pentane/Et_2O 1:2). **Optical rotation**: $[\alpha]_D^{27}$ = +29.8° (c = 1.26, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3425, 2930, 2857, 1719, 1672, 1626, 1463, 1387, 1250, 1100, 1068, 887, 835, 774 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 9.97 (s, 1H), 5.82 (d, *J* = 1.5 Hz, 1H), 3.92 (s, 1H), 3.58 (td, *J* = 10.4, 4.5 Hz, 1H), 2.79 (dd, *J* = 15.8, 1.9 Hz, 1H), 2.53 – 2.46 (m, 1H), 2.47 (d, *J* = 16.1 Hz, 1H), 2.32 (ddd, *J* = 14.5, 4.5, 2.7 Hz, 1H), 2.18 (d, *J* = 14.5 Hz, 1H), 2.06 (dtd, *J* = 12.5, 4.9, 2.7 Hz, 1H), 1.74 (d, *J* = 14.5 Hz, 1H), 1.44 (dddd, *J* = 14.9, 12.4, 10.9, 4.5 Hz, 1H), 1.36 – 1.30 (m, 1H), 1.29 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 202.7, 197.0, 171.1, 120.6, 76.0, 71.5, 50.9, 49.3, 47.7, 40.2, 36.3, 31.7, 26.0 (3C), 21.2, 18.2, 11.3, -3.9, -4.6. **HRMS** (ESI) Exact mass calculated for $C_{20}H_{35}O_4Si^+$ $[M+H]^+$: 367.22991, found: 367.23002.



7*S*-/7*R*-**2.86**, *dr* 5:3 — **2.103**, 68 %, *dr* 5:3 (7*S*/7*R*)

(4a*R*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-4a,5-dimethyl-3-((triethylsilyl)oxy)-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.103): To a stirred mixture of 7*S*- and 7*R*-**2.86** (29.0 mg, 89.4 µmol, 1.0 equiv., *dr* 5:3) in CH_2Cl_2 (1.0 mL) at rt were added imidazole (18.3 mg, 0.268 mmol, 3.0 equiv.) and TESCl (27 µL, 0.161 mmol, 1.8 equiv.). The mixture was stirred for 90 min, before it was quenched by addition of sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 15:1) to give **2.103** (26.6 mg, 60.6 µmol, 68 %, *dr* 5:3) as a colorless oil.

TLC: R_f = 0.47 (SiO_2, pentane/Et_2O 10:1). **FTIR** (neat): $\tilde{\nu}$ = 2953, 2929, 2877, 2857, 1698, 1625, 1462, 1252, 1147, 1099, 1077, 889, 835, 774, 743 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those from the minor diastereoisomer with [b]) δ = 5.72[a] (d, *J* = 1.4 Hz, 1H), 5.69[b] (d, *J* = 1.6 Hz, 1H), 4.28[b] (dd, *J* = 13.4, 5.3 Hz, 1H), 4.14[a] (dd, *J* = 9.0, 4.6 Hz, 1H), 3.63[a] (ddd, *J* = 10.9, 9.7, 4.8 Hz, 1H), 3.55[b] (td, *J* = 10.5, 4.4 Hz, 1H), 2.48[a] (tdd, *J* = 14.4, 5.0, 1.6 Hz, 1H), 2.37[b] (tdd, *J* = 14.3, 5.0, 1.7 Hz, 1H), 2.29[b] (ddd, *J* = 14.5, 4.6, 2.1 Hz, 1H), 2.23[a] (ddd, *J* = 13.5, 4.6, 2.7 Hz, 1H), 2.16[b] (dd, *J* = 12.9, 5.3 Hz, 1H), 2.11[a] (dtd, *J* = 12.5, 4.9, 2.7 Hz, 1H), 2.05 – 1.96[a+b] (m, 2H), 1.91[a] (dd, *J* = 14.2, 9.0 Hz, 1H), 1.77[b] (t, *J* = 13.2 Hz, 1H), 1.54 – 1.33[a+b] (m, 4H), 1.19[b] (s, 3H), 1.16[a] (s, 3H), 1.04[a] (d, *J* = 6.7 Hz, 3H), 0.99[b] (d, *J* = 6.2 Hz, 3H), 0.97[a+b] (t, *J* = 4.0 Hz, 18H), 0.90[a] (s, 9H), 0.89[b] (s, 9H), 0.69 – 0.60[a+b] (m, 12H), 0.10 – 0.05[a+b] (m, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those from the minor diastereoisomer with [b]) δ = 198.5[b], 197.9[a], 169.5[a], 167.7[b], 122.6[b], 121.5[a], 72.2[a], 71.5[b], 70.7[a], 70.4[b], 50.7[b], 48.2[a], 46.2[b], 43.0[a], 41.3[b], 40.5[a], 37.4[a], 35.9[b], 31.3[a], 31.1[b], 29.9[b], 26.0[a] (3C), 26.0[b] (3C), 21.9[a], 18.2[a], 18.1[b], 12.1[a], 11.0[b], 7.0[b] (3C), 6.9[a] (3C), 5.1[b] (3C), 4.9[a] (3C), -3.9[a+b], -4.5[a], -4.5[b]. **HRMS** (ESI) Exact mass calculated for $C_{24}H_{47}O_3Si_2^+$ $[M+H]^+$: 439.30582, found: 439.30569.



7*S*-/7*R*-**2.86**, *dr* 3:2 — 7*S*-**2.105**, 56 % — 7*R*-**2.105**, 28 %

To a mixture of 7*S*- and 7*R*-**2.86** (291 mg, 0.897 mmol, 1.0 equiv., *dr* 3:2) and DIPEA (890 µL, 5.38 mmol, 6.0 equiv.) in CH_2Cl_2 (14 mL) was added SEMCl (476 µL, 2.69 mmol, 3.0 equiv.). The mixture was stirred at rt for 29 h, before it was diluted with CH_2Cl_2 and sat. aq. $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 3:1) to give 7*S*-**2.105** (227 mg, 0.499 mmol, 56 %) and 7*R*-**2.105** (113 mg, 0.248 mmol, 28 %) both as colorless oils.

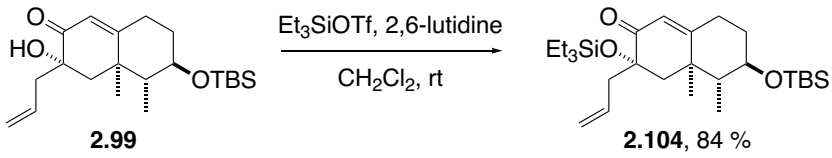
(3*S*,4a*R*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-4a,5-dimethyl-3-((2-(trimethylsilyl)-ethoxy)methoxy)-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (7*S*-**2.105):**

TLC: R_f = 0.57 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{24}$ = –81.8° (c = 0.34, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2953, 1694, 1472, 1250, 1098, 1076, 1031, 887, 835, 774 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.75 (d, *J* = 1.3 Hz, 1H), 4.83 (d, *J* = 6.9 Hz, 1H), 4.79 (d, *J* = 6.9 Hz,

1H), 4.18 (dd, *J* = 10.0, 4.7 Hz, 1H), 3.72 – 3.66 (m, 1H), 3.66 – 3.58 (m, 2H), 2.53 – 2.45 (m, 1H), 2.23 (ddd, *J* = 13.4, 4.7, 2.7 Hz, 1H), 2.15 – 2.09 (m, 2H), 1.90 (dd, *J* = 14.1, 10.0 Hz, 1H), 1.63 (dq, *J* = 9.5, 6.7 Hz, 1H), 1.48 – 1.38 (m, 1H), 1.15 (s, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.97 – 0.91 (m, 2H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.02 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 197.3, 170.2, 121.7, 94.4, 73.0, 72.2, 65.6, 47.8, 40.6, 40.1, 37.6, 31.2, 26.0 (3C), 22.0, 18.3, 18.2, 12.2, -1.3 (3C), -3.8, -4.6. **HRMS** (ESI) Exact mass calculated for $C_{24}H_{46}NaO_4Si_2^+$ $[M+Na]^+$: 477.28268, found: 477.28318.

3*R*,4a*R*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-4a,5-dimethyl-3-((2-(trimethylsilyl)-ethoxy)methoxy)-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (7*R*-2.105):

TLC: R_f = 0.38 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{25}$ = +96.0° (c = 0.87, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2952, 2930, 2886, 2858, 1694, 1625, 1463, 1250, 1220, 1189, 1127, 1099, 1076, 1057, 1040, 889, 862, 834, 774, 693 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.72 (d, *J* = 1.6 Hz, 1H), 4.91 (d, *J* = 7.0 Hz, 1H), 4.87 (d, *J* = 7.0 Hz, 1H), 4.30 (dd, *J* = 13.8, 5.3 Hz, 1H), 3.70 (dtd, *J* = 32.2, 9.9, 6.3 Hz, 2H), 3.56 (td, *J* = 10.5, 4.4 Hz, 1H), 2.44 – 2.30 (m, 2H), 2.27 (dd, *J* = 12.8, 5.4 Hz, 1H), 2.07 – 1.99 (m, 1H), 1.74 (t, *J* = 13.3 Hz, 1H), 1.51 – 1.40 (m, 1H), 1.40 – 1.33 (m, 1H), 1.21 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.97 – 0.90 (m, 2H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.03 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 197.9, 168.4, 122.8, 94.7, 73.0, 71.5, 65.6, 50.7, 43.4, 41.3, 35.8, 31.1, 26.0 (3C), 18.3, 18.2, 18.2, 11.0, -1.2 (3C), -3.9, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{24}H_{46}NaO_4Si_2^+$ $[M+Na]^+$: 477.28268, found: 477.28318.

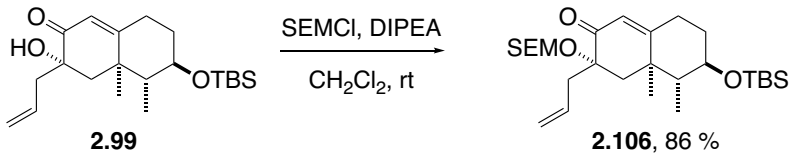


2.99 **2.104**, 84 %

(3*S*,4a*R*,5*R*,6*R*)-3-Allyl-6-((*tert*-butyldimethylsilyl)oxy)-4a,5-dimethyl-3-((triethylsilyl)-oxy)-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.104): To a stirred solution of **2.99** (24.0 mg, 65.8 µmol, 1.0 equiv.) in CH_2Cl_2 (1.5 mL) at 0°C were added 2,6-lutidine (23 µL, 0.197 mmol, 3.0 equiv.) and TESOTf (30 µL, 0.132 mmol, 2.0 equiv.). The mixture was stirred for 1 h and then quenched by addition of sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column

chromatography (pentane/Et_2O 10:1) to give **2.104** (26.5 mg, 55.3 µmol, 84 %) as a colorless oil.

TLC: R_f = 0.61 (SiO_2, pentane/Et_2O 10:1). **Optical rotation**: $[\alpha]_D^{26}$ = +35.1° (c = 0.82, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2953, 2878, 1677, 1628, 1462, 1251, 1127, 1079, 1041, 1007, 914, 890, 836, 774, 743 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.76 (d, *J* = 1.5 Hz, 1H), 5.70 (ddt, *J* = 20.2, 9.6, 7.2 Hz, 1H), 5.08 – 5.05 (m, 1H), 5.04 (s, 1H), 3.57 (td, *J* = 10.4, 4.4 Hz, 1H), 2.55 (dd, *J* = 13.8, 7.0 Hz, 1H), 2.48 – 2.39 (m, 2H), 2.27 (ddd, *J* = 14.4, 4.5, 2.7 Hz, 1H), 2.08 (d, *J* = 14.7 Hz, 1H), 2.06 – 2.01 (m, 1H), 1.58 (d, *J* = 14.6 Hz, 1H), 1.58 (s, 1H), 1.41 (dddd, *J* = 15.0, 12.3, 10.9, 4.5 Hz, 1H), 1.24 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.93 – 0.82 (m, 18H), 0.56 (q, *J* = 7.6 Hz, 6H), 0.06 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 197.3, 169.5, 134.1, 122.4, 118.3, 75.2, 71.6, 51.4, 47.8, 42.6, 39.7, 36.3, 31.6, 26.0 (3C), 20.5, 18.2, 11.3, 7.1 (3C), 6.3 (3C), -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{27}H_{51}O_3Si_2^+$ $[M+H]^+$: 479.33712, found: 479.33737.

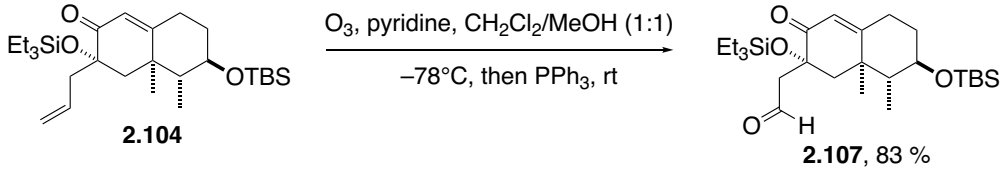


2.99 **2.106**, 86 %

(3*S*,4a*R*,5*R*,6*R*)-3-Allyl-6-((*tert*-butyldimethylsilyl)oxy)-4a,5-dimethyl-3-((2-(trimethylsilyl)ethoxy)methoxy)-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.106): To a stirred solution of **2.99** (25.0 mg, 68.6 µmol, 1.0 equiv.) in CH_2Cl_2 (1.5 mL) at rt were added SEMCl (49 µL, 0.274 mmol, 4.0 equiv.) and DIPEA (68 µL, 0.412 mmol, 6.0 equiv.). The mixture was stirred for 15 h at rt and then quenched by addition of sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 10:1) to give **2.106** (29.3 mg, 59.2 µmol, 86 %) as a colorless oil.

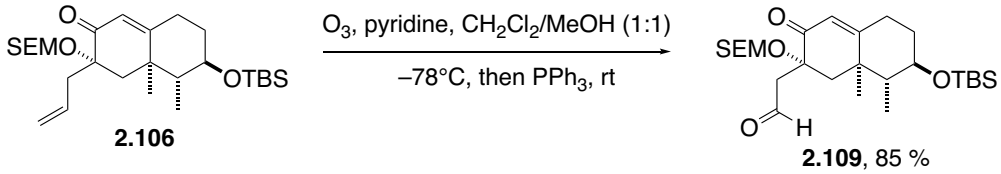
TLC: R_f = 0.57 (SiO_2, pentane/Et_2O 5:1). **Optical rotation**: $[\alpha]_D^{24}$ = +26.8° (c = 1.47, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2952, 2886, 2858, 1675, 1630, 1463, 1438, 1361, 1250, 1197, 1126, 1101, 1075, 1011, 939, 915, 889, 860, 835, 774, 697, 616 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.78 (d, *J* = 1.4 Hz, 1H), 5.76 – 5.65 (m, 1H), 5.11 (s, 1H), 5.09 – 5.05 (m, 1H), 4.66 (d, *J* = 6.9 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 1H), 3.58 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.56 – 3.41 (m, 2H), 2.70 (ddt, *J* = 14.6, 7.2, 1.3 Hz, 1H), 2.44 (tdd, *J* = 14.4, 5.1, 1.6 Hz, 1H), 2.35 (ddt, *J* = 14.6, 7.1, 1.3

Hz, 1H), 2.30 – 2.23 (m, 1H), 2.26 (d, *J* = 14.8 Hz, 1H), 2.05 (dtd, *J* = 12.3, 4.8, 2.6 Hz, 1H), 1.54 (d, *J* = 14.9 Hz, 1H), 1.42 (dddd, *J* = 14.4, 12.5, 10.9, 4.5 Hz, 1H), 1.29 (s, 3H), 1.27 – 1.20 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.87 – 0.78 (m, 2H), 0.07 (s, 3H), 0.06 (s, 3H), -0.02 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 196.7, 168.6, 133.4, 122.2, 118.7, 89.7, 76.9, 71.6, 65.9, 51.9, 46.6, 39.5, 37.4, 36.4, 31.6, 26.0 (3C), 20.6, 18.2, 18.0, 11.1, -1.3 (3C), -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{27}H_{50}NaO_4Si_2^+$ $[M+Na]^+$: 517.31398, found: 517.31380.



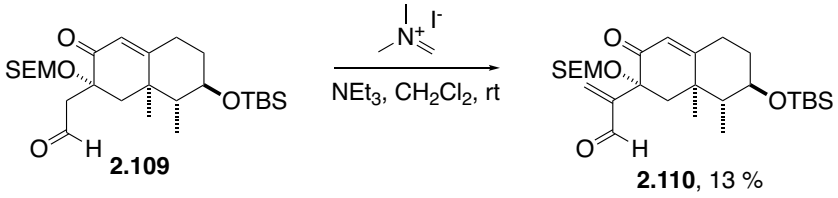
2-((2*R*,7*R*,8*R*,8a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-8,8a-dimethyl-3-oxo-2-((triethylsilyl)-oxy)-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)acetaldehyde (2.107): A solution of **2.104** (15.2 mg, 31.7 µmol, 1.0 equiv.), pyridine (10 µL, 0.127 mmol, 4.0 equiv.) and Sudan III (spatula tip) in CH_2Cl_2/MeOH (1.6 mL, 1:1) was cooled to –78°C and O_3 was bubbled through the solution until the red color disappeared (1 min). The reaction was purged with O_2 and N_2. PPh_3 (16.6 mg, 63.4 µmol, 2.0 equiv.) was added and the mixture was allowed to warm up to rt. After stirring for 60 min, the solvent was removed by evaporation and the residue was subjected to flash column chromatography (pentane/Et_2O 7:1) to give **2.107** (12.6 mg, 26.2 µmol, 83 %) as a colorless oil.

TLC: R_f = 0.55 (SiO_2, pentane/Et_2O 5:1). **Optical rotation**: $[\alpha]_D^{24}$ = +23.8° (c = 0.63, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2954, 2879, 1725, 1677, 1626, 1462, 1387, 1361, 1251, 1128, 1072, 1007, 955, 921, 888, 836, 774, 745, 726 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.72 (t, *J* = 2.3 Hz, 1H), 5.82 (d, *J* = 1.5 Hz, 1H), 3.57 (ddd, *J* = 10.8, 9.8, 4.5 Hz, 1H), 2.86 (dd, *J* = 15.7, 2.3 Hz, 1H), 2.77 (dd, *J* = 15.7, 2.5 Hz, 1H), 2.47 (tdd, *J* = 14.4, 5.1, 1.7 Hz, 1H), 2.31 (ddd, *J* = 14.4, 4.5, 2.6 Hz, 1H), 2.22 (d, *J* = 14.5 Hz, 1H), 2.06 (dtd, *J* = 12.4, 4.9, 2.6 Hz, 1H), 1.74 (d, *J* = 14.4 Hz, 1H), 1.51 – 1.39 (m, 1H), 1.32 – 1.23 (m, 1H), 1.27 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.91 – 0.86 (m, 18H), 0.60 – 0.53 (m, 6H), 0.06 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 201.1, 195.8, 170.3, 121.7, 74.4, 71.4, 51.5, 51.4, 48.9, 39.9, 36.3, 31.8, 26.0 (3C), 20.6, 18.2, 11.2, 7.1 (3C), 6.2 (3C), -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{26}H_{48}NaO_4Si_2^+$ $[M+Na]^+$: 503.29833, found: 503.29846.



2-((2*R*,7*R*,8*R*,8a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-8,8a-dimethyl-3-oxo-2-((2-(trimethylsilyl)ethoxy)methoxy)-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)acetaldehyde (2.109): A solution of **2.106** (29.3 mg, 59.2 µmol, 1.0 equiv.), pyridine (20 µL, 0.237 mmol, 4 equiv.) and Sudan III (traces) in CH_2Cl_2/MeOH (2.0 mL, 1:1) was cooled to –78°C and O_3 was bubbled through the solution until the red color disappeared (<1 min). The reaction mixture was purged with O_2 and N_2. PPh_3 (31 mg, 0.118 mmol, 2.0 equiv.) was added and the mixture was allowed to warm up to rt. After stirring for 60 min, the solvent was removed by evaporation and the residue was subjected to flash column chromatography (pentane/Et_2O 4:1) to give **2.109** (24.9 mg, 50.1 µmol, 85 %) as a colorless oil.

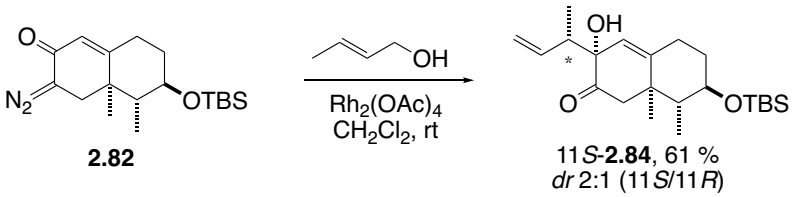
TLC: R_f = 0.19 (SiO_2, pentane/Et_2O 5:1). **Optical rotation**: $[\alpha]_D^{23}$ = +9.7° (c = 1.24, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2952, 2888, 2857, 1723, 1675, 1628, 1463, 1438, 1386, 1361, 1250, 1196, 1124, 1100, 1071, 1007, 939, 888, 860, 835, 774, 693 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.76 (t, *J* = 2.3 Hz, 1H), 5.81 (d, *J* = 1.4 Hz, 1H), 4.68 (s, 2H), 3.62 – 3.49 (m, 3H), 2.93 (dd, *J* = 16.2, 2.3 Hz, 1H), 2.80 (dd, *J* = 16.2, 2.3 Hz, 1H), 2.45 (tdd, *J* = 14.4, 5.1, 1.6 Hz, 1H), 2.38 (d, *J* = 14.8 Hz, 1H), 2.29 (ddd, *J* = 14.3, 4.6, 2.7 Hz, 1H), 2.06 (dtd, *J* = 12.3, 4.9, 2.6 Hz, 1H), 1.74 (d, *J* = 14.8 Hz, 1H), 1.44 (dddd, *J* = 14.4, 12.5, 10.9, 4.5 Hz, 1H), 1.29 (s, 3H), 1.29 – 1.24 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.87 – 0.83 (m, 2H), 0.06 (s, 3H), 0.06 (s, 3H), -0.01 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 201.0, 195.0, 169.6, 121.4, 90.1, 76.7, 71.4, 66.2, 51.8, 47.2, 47.1, 39.8, 36.3, 31.7, 25.9 (3C), 20.7, 18.2, 18.0, 11.1, -1.3 (3C), -3.8, -4.6. **HRMS** (ESI) Exact mass calculated for $C_{26}H_{48}NaO_5Si_2^+$ $[M+Na]^+$: 519.29325, found: 519.29411.



2-((2*R*,7*R*,8*R*,8a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-8,8a-dimethyl-3-oxo-2-((2-(trimethylsilyl)ethoxy)methoxy)-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)acrylaldehyde (2.110): Eschenmoser's salt (66.3 mg, 0.351 mmol, 3.0 equiv.) was added to a solution of **2.109**

(58.1 mg, 0.117 mmol, 1.0 equiv.) and DIPEA (116 µL, 0.702 mmol, 6.0 equiv.) in CH_2Cl_2 (3.0 mL) at rt. The mixture was stirred for 4.5 h and then quenched by addition of sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to give **2.110** (7.7 mg, 15.1 µmol, 13 %) as a colorless oil.

TLC: R_f = 0.38 (SiO_2, pentane/Et_2O 2:1). **Optical rotation**: $[\alpha]_D^{24}$ = +33.9° (c = 0.39, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3675, 2954, 2900, 1700, 1676, 1630, 1384, 1292, 1250, 1099, 1074, 1005, 969, 939, 889, 861, 836, 774, 692 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.57 (s, 1H), 6.60 (s, 1H), 6.26 (s, 1H), 5.87 (d, *J* = 1.6 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.58 (d, *J* = 6.5 Hz, 1H), 3.63 – 3.48 (m, 3H), 2.47 (tdd, *J* = 14.4, 5.1, 1.7 Hz, 1H), 2.33 (ddd, *J* = 14.3, 4.6, 2.6 Hz, 1H), 2.16 (d, *J* = 14.7 Hz, 1H), 2.06 (dtd, *J* = 12.2, 4.8, 2.5 Hz, 1H), 2.01 (d, *J* = 14.5 Hz, 1H), 1.54 – 1.47 (m, 1H), 1.40 – 1.35 (m, 1H), 1.34 (s, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.87 – 0.78 (m, 2H), 0.07 (s, 3H), 0.06 (s, 3H), -0.01 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 193.5, 193.0, 168.6, 150.9, 135.4, 122.6, 90.7, 79.8, 71.6, 66.5, 51.4, 48.1, 39.5, 36.2, 31.7, 26.0 (3C), 21.2, 18.2, 18.1, 11.2, -1.3 (3C), -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{27}H_{48}NaO_5Si_2^+$ $[M+Na]^+$: 531.29325, found: 531.29337.



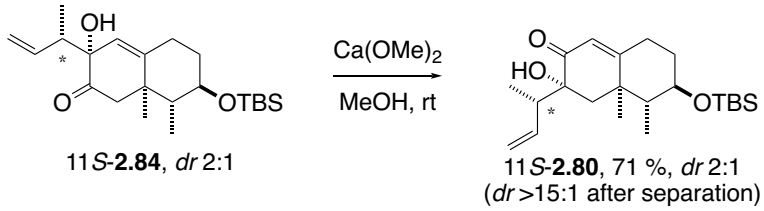
2.82

11*S*-**2.84**, 61 %
dr 2:1 (11*S*/11*R*)

(3*R*,7*R*,8*R*,8a*R*)-3-((*S*)-But-3-en-2-yl)-7-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-8,8a-dimethyl-3,5,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one (11*S*-**2.84**):** To a solution of $Rh_2(OAc)_4$ (36.2 mg, 5 mol%) and *trans*-2-buten-1-ol (2.46 g, 32.8 mmol, 20.0 equiv.) in CH_2Cl_2 (35.0 mL) at rt was added dropwise a solution of **2.82** (550 mg, 1.64 mmol, 1.0 equiv.) in CH_2Cl_2 (10.0 mL) over a period of 15 min and the mixture was stirred for another 1 h at rt. The solvent was evaporated and the residue purified by flash column chromatography (pentane/Et_2O 6:1) to give 11*S*-**2.84** (418 mg, 1.10 mmol, 67 %, *dr* 2:1) as colorless oil.

TLC: R_f = 0.67 (SiO_2, pentane/Et_2O 3:1). **FTIR** (neat): $\tilde{\nu}$ = 3488, 2931, 2857, 1718, 1461, 1386, 1293, 1253, 1145, 1105, 1071, 1006, 890, 837, 775, 675 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those from the minor diastereoisomer

with [b]) δ = 5.83[b] (ddd, *J* = 17.2, 10.3, 8.6 Hz, 1H), 5.71[a] (ddd, *J* = 17.1, 10.5, 8.2 Hz, 1H), 5.43[a] (d, *J* = 1.5 Hz, 1H), 5.35[b] (d, *J* = 1.4 Hz, 1H), 5.12[b] (ddd, *J* = 10.2, 1.8, 0.6 Hz, 1H), 5.07[b] (ddd, *J* = 17.2, 1.8, 0.9 Hz, 1H), 5.00[a] (ddd, *J* = 10.5, 1.7, 0.8 Hz, 1H), 4.98[a] (dt, *J* = 17.2, 1.3 Hz, 1H), 3.60[a+b] (s, 2H), 3.49 – 3.41[a+b] (m, 2H), 2.62[b] (d, *J* = 12.3 Hz, 1H), 2.61[a] (d, *J* = 12.2 Hz, 1H), 2.55 – 2.48[a] (m, 1H), 2.49[b] (d, *J* = 12.4 Hz, 1H), 2.48 – 2.41[b] (m, 1H), 2.44[a] (d, *J* = 12.2 Hz, 1H), 2.27 – 2.16[a+b] (m, 4H), 2.03 – 1.96[a+b] (m, 2H), 1.55 – 1.37[a+b] (m, 4H), 1.15[a] (d, *J* = 6.8 Hz, 3H), 0.95[b] (s, 3H), 0.95[a] (s, 30H), 0.93[b] (d, *J* = 6.8 Hz, 3H), 0.92[a] (d, *J* = 6.8 Hz, 3H), 0.91[b] (d, *J* = 6.9 Hz, 3H), 0.90[a+b] (s, 18H), 0.07[a+b] (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those from the minor diastereoisomer with [b]) δ = 212.0[b], 211.4[a], 144.8[a], 144.4[b], 138.6[a], 138.5[b], 124.5[b], 123.9[a], 116.7[b], 115.8[a], 78.6[a], 78.3[b], 72.1[b], 72.1[a], 51.1[b], 51.0[a], 49.7[b], 49.6[a], 49.0[b], 48.7[a], 46.8[a], 46.7[b], 36.8[b], 36.7[a], 30.2[a], 30.1[b], 26.0[a+b] (6C), 19.8[a+b], 18.2[b], 18.2[a], 15.0[b], 13.6[a], 11.4[a+b], -3.9[a+b], -4.6[a+b]. **HRMS** (ESI) Exact mass calculated for $C_{22}H_{38}NaO_3Si^+$ $[M+Na]^+$: 401.2482, found: 401.2486.



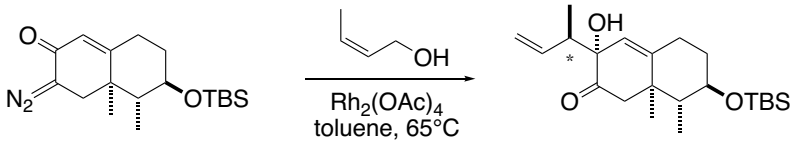
11*S*-**2.84**, *dr* 2:1

11*S*-**2.80**, 71 %, *dr* 2:1 (*dr* >15:1 after separation)

(3*R*,4a*R*,5*R*,6*R*)-3-((*S*)-But-3-en-2-yl)-6-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (11*S*-**2.80):** A mixture of 11*S*- and 11*R*-**2.84** (324 mg, 0.856 mmol, 1.0 equiv., *dr* 2:1) and $Ca(OMe)_2$ (180 mg, 1.71 mmol, 2.0 equiv.) in MeOH (20.0 ml) was stirred for 44 h at rt. Sat. aq. NH_4Cl solution was added slowly and the mixture was diluted with H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 3:1) to give 11*S*-**2.80** (230 mg, 0.608 mmol, 71 %, *dr* 2:1) as a colorless solid. Purification by additional flash column chromatography (pentane/Et_2O 4:1) gave access to diastereomerically pure 11*S*-**2.80**.

M.p. = 163.1 – 165.8°C. TLC: R_f = 0.38 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{22}$ = –9.0° (c = 0.46, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3385, 2957, 2855, 1656, 1622, 1461, 1249, 1100, 1069, 1004, 914, 891, 836, 772, 620. cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.87 – 5.77 (m, 1H), 5.81 (d, *J* = 1.9 Hz, 1H), 5.13 (dd, *J* = 10.4, 1.7 Hz, 1H), 5.06 (dt, *J* = 17.3, 1.3 Hz, 1H),

3.57 (ddd, *J* = 10.9, 9.7, 4.5 Hz, 1H), 2.98 (s, 1H), 2.62 (p, *J* = 7.1 Hz, 1H), 2.50 (tdd, *J* = 14.4, 4.9, 2.0 Hz, 1H), 2.30 (ddd, *J* = 14.3, 4.4, 2.9 Hz, 1H), 2.16 (d, *J* = 14.8 Hz, 1H), 2.06 (dtd, *J* = 12.5, 4.8, 2.8 Hz, 1H), 1.70 (d, *J* = 14.8 Hz, 1H), 1.67 – 1.59 (m, 1H), 1.52 – 1.40 (m, 1H), 1.14 (s, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 201.0, 170.6, 139.1, 121.3, 117.2, 75.9, 72.2, 48.4, 45.4, 42.0, 40.2, 36.3, 31.4, 26.0 (3C), 23.5, 18.2, 14.2, 12.4, -3.8, -4.6. **HRMS** (ESI) Exact mass calculated for $C_{22}H_{39}O_3Si^+$ $[M+H]^+$: 379.26630, found: 379.26663; for $C_{22}H_{38}NaO_3Si^+$ $[M+Na]^+$: 401.24824, found: 401.24859.

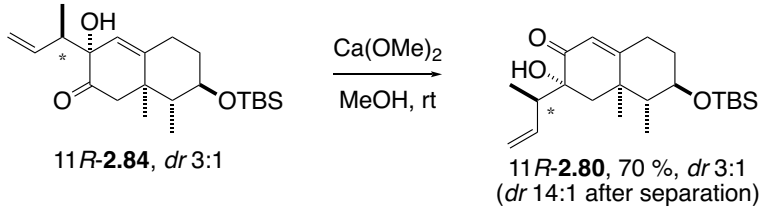


2.82 11*R*-**2.84**, 60 %
dr 3:1 (11*R*/11*S*)

(3*R*,7*R*,8*R*,8a*R*)-3-((*R*)-But-3-en-2-yl)-7-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-8,8a-dimethyl-3,5,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one (11*R*-**2.84**):** To a solution of $Rh_2(OAc)_4$ (13.9 mg, 3.5 mol%) and *cis*-2-buten-1-ol (1.29 g, 17.9 mmol, 20 equiv.) in toluene (4.5 mL) at 65°C was added dropwise a solution of **2.82** (300 mg, 0.897 mmol, 1.0 equiv.) in toluene (4.5 mL) over a period of 8 min and the mixture was stirred for additional 40 min at this temperature. The solvent was evaporated and the residue purified by flash column chromatography (pentane/Et_2O 6:1) to give 11*R*-**2.84** (204 mg, 0.539 mmol, 60 %, *dr* 3:1) as a colorless solid.

M.p. = 84.2 – 86.1°C. TLC: R_f = 0.67 (SiO_2, pentane/Et_2O 3:1). **FTIR** (neat): $\tilde{\nu}$ = 3488, 2931, 2857, 1718, 1461, 1386, 1293, 1253, 1145, 1105, 1071, 1006, 890, 837, 775, 675 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those from the minor diastereoisomer with [b]) δ = 5.83[a] (ddd, *J* = 17.2, 10.3, 8.6 Hz, 1H), 5.71[b] (ddd, *J* = 17.1, 10.5, 8.2 Hz, 1H), 5.43[b] (d, *J* = 1.5 Hz, 1H), 5.35[a] (d, *J* = 1.4 Hz, 1H), 5.12[a] (ddd, *J* = 10.2, 1.8, 0.6 Hz, 1H), 5.07[a] (ddd, *J* = 17.2, 1.8, 0.9 Hz, 1H), 5.00[b] (ddd, *J* = 10.5, 1.7, 0.8 Hz, 1H), 4.98[b] (dt, *J* = 17.2, 1.3 Hz, 1H), 3.60[a+b] (s, 2H), 3.49 – 3.41[a+b] (m, 2H), 2.62[a] (d, *J* = 12.3 Hz, 1H), 2.61[b] (d, *J* = 12.2 Hz, 1H), 2.55 – 2.48[b] (m, 1H), 2.49[a] (d, *J* = 12.4 Hz, 1H), 2.48 – 2.41[a] (m, 1H), 2.44[b] (d, *J* = 12.2 Hz, 1H), 2.27 – 2.16[a+b] (m, 4H), 2.03 – 1.96[a+b] (m, 2H), 1.55 – 1.37[a+b] (m, 4H), 1.15[b] (d, *J* = 6.8 Hz, 3H), 0.95[a] (s, 3H), 0.95[b] (s, 30H), 0.93[a] (d, *J* = 6.8 Hz, 3H), 0.92[b] (d, *J* = 6.8 Hz, 3H), 0.91[a] (d, *J* = 6.9 Hz, 3H), 0.90[a+b] (s, 18H), 0.07[a+b] (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those

from the minor diastereoisomer with [b]) δ = 212.0[a], 211.4[b], 144.8[b], 144.4[a], 138.6[b], 138.5[a], 124.5[a], 123.9[b], 116.7[a], 115.8[b], 78.6[b], 78.3[a], 72.1[a], 72.1[b], 51.1[a], 51.0[b], 49.7[a], 49.6[b], 49.0[a], 48.7[b], 46.8[b], 46.7[a], 36.8[a], 36.7[b], 30.2[b], 30.1[a], 26.0[a+b] (6C), 19.8[a+b], 18.2[a], 18.2[b], 15.0[a], 13.6[b], 11.4[a+b], -3.9[a+b], -4.6[a+b]. **HRMS** (ESI) Exact mass calculated for $C_{22}H_{38}NaO_3Si^+$ $[M+Na]^+$: 401.2482, found: 401.2486.

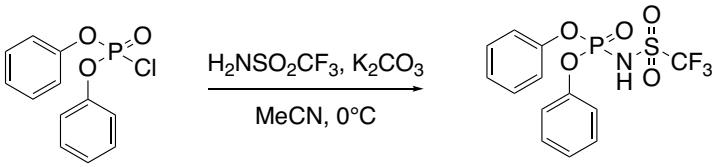


11*R*-**2.84**, *dr* 3:1

11*R*-**2.80**, 70 %, *dr* 3:1
(*dr* 14:1 after separation)

(3*R*,4a*R*,5*R*,6*R*)-3-((*R*)-But-3-en-2-yl)-6-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (11*R*-**2.80):** A mixture of 11*R*- and 11*S*-**2.84** (67.3 mg, 0.18 mmol, 1.0 equiv., *dr* 3:1) and $Ca(OMe)_2$ (37.5 mg, 0.356 mmol, 2.0 equiv.) in MeOH (6.0 ml) was stirred for 45 h at rt. Sat. aq. NH_4Cl solution was added slowly and the mixture was diluted with H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 3:1) to give 11*R*-**2.80** (47.2 mg, 0.13 mmol, 70 %, *dr* 3:1) as a colorless solid. Purification by additional flash column chromatography (pentane/Et_2O 4:1) gave access to desired 11*R*-**2.80** with a *dr* 14:1.

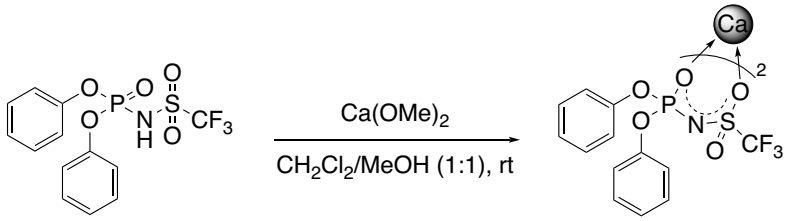
M.p. = 160.4 – 162.2°C. TLC: R_f = 0.33 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{25}$ = +20.2° (c = 0.81, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3388, 2954, 2855, 1655, 1623, 1461, 1360, 1248, 1131, 1100, 1071, 1007, 916, 890, 835, 772, 703, 595 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.87 – 5.73 (m, 2H), 5.14 – 4.99 (m, 2H), 3.59 (td, *J* = 10.5, 4.4 Hz, 1H), 2.73 (s, 1H), 2.73 – 2.62 (m, 1H), 2.50 (tdd, *J* = 14.5, 5.0, 2.0 Hz, 1H), 2.31 (ddd, *J* = 14.4, 4.4, 2.9 Hz, 1H), 2.11 (d, *J* = 14.8 Hz, 1H), 2.10 – 2.02 (m, 1H), 1.72 (d, *J* = 14.9 Hz, 1H), 1.61 – 1.50 (m, 1H), 1.54 – 1.39 (m, 1H), 1.16 (s, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 200.4, 170.1, 138.7, 121.6, 116.5, 76.1, 72.3, 48.6, 44.9, 41.1, 40.1, 36.3, 31.4, 26.0 (3C), 23.3, 18.2, 14.4, 12.3, -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{22}H_{39}O_3Si^+$ $[M+H]^+$: 379.26630, found: 379.26612.



6.6 **2.112**, 60 %

Diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (2.112): Diphenyl chlorophosphate (**6.6,** 1.15 mL, 5.54 mmol, 1.1 equiv.) was added to a mixture of trifluoromethanesulfonamide (0.752 g, 5.04 mmol, 1.0 equiv.) and K_2CO_3 (0.697 g, 5.04 mmol, 1.0 equiv.) in MeCN (8.0 mL) at 0°C. The mixture was allowed to warm to rt and stirred at this temperature for 15 h. The solution was diluted with H_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 x) and the combined organics were washed with sat. aq. $NaHCO_3$ and aqueous HCl (6 M) solution. After the HCl layer was re-extracted with Et_2O, the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH 10:1) to give **2.112** (1.15 g, 3.02 mmol, 60 %) as a colorless solid.

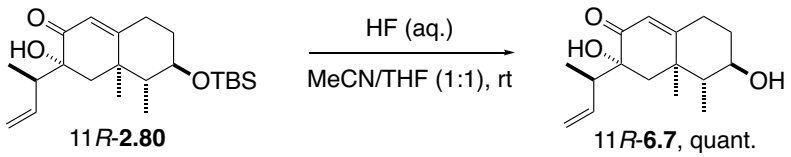
M.p. = 59.5 – 61.9C. TLC: R_f = 0.68 (SiO_2, CH_2Cl_2/MeOH 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.34 – 7.30 (m, 4H), 7.23 – 7.18 (m, 6H), 4.30 (*br*, s, 1H), 3.45 (s, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -77.2. **^{31}P NMR** (162 MHz, $CDCl_3$) δ = -16.1. **HRMS** (ESI) Exact mass calculated for $C_{13}H_{12}F_3NO_5PS^+$ $[M+H]^+$: 382.01204, found: 382.01222.



2.112 **2.113**, quant.

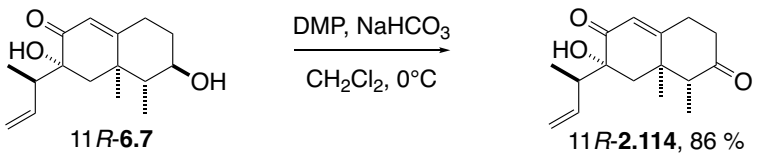
Calcium salt of 2.113: A solution of **2.112** (100 mg, 0.262 mmol, 1.0 equiv.) and $Ca(OMe)_2$ (13.4 mg, 0.131 mmol, 0.5 equiv.) in CH_2Cl_2/MeOH (1:1, 10.0 ml) was stirred at rt for 64 h. Evaporation of the solvent gave **2.113** as a colorless solid.

M.p. = 210.5 – 215.7°C. TLC: R_f = 0.68 (SiO_2, CH_2Cl_2/MeOH 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.24 – 7.18 (m, 4H), 7.12 – 7.06 (m, 6H), 3.37 (s, 1H), 2.14 (*br*, s, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -79.4. **^{31}P NMR** (162 MHz, $CDCl_3$) δ = -13.3.



(3*R*,4a*R*,5*R*,6*R*)-3-((*R*)-But-3-en-2-yl)-3,6-dihydroxy-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (11*R*-**6.7):** To a solution of 11*R*-**2.80** (78.0 mg, 0.206 mmol, 1.0 equiv.) in MeCN/THF (1:1, 3.0 mL) was added a solution of HF (48 % in H_2O, 87 µL, 2.06 mmol, 10 equiv.). The mixture was stirred for 10 h at rt, before additional HF (21 µL, 0.50 mmol, 2.4 equiv.) was added and stirring continued for 14 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution and extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Crude 11*R*-**6.7** (54.5 mg, 0.206 mmol, quant., *dr* 14:1) was obtained as colorless oil and used without further purification in the next step. For analytical purposes, 11*R*-**6.7** was purified by flash column chromatography (pentane/Et_2O 1:2) and obtained as a colorless oil.

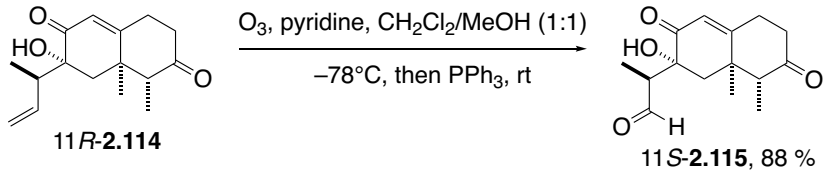
TLC: R_f = 0.23 (SiO_2, pentane/Et_2O 1:2). **Optical rotation**: $[\alpha]_D^{23}$ = +30.6° (c = 1.11, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3424, 2972, 2940, 1660, 1455, 1384, 1241, 1128, 1093, 1029, 914, 886, 583 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.84 (d, *J* = 1.9 Hz, 1H), 5.78 (ddd, *J* = 17.2, 10.3, 8.0 Hz, 1H), 5.09 – 4.97 (m, 2H), 3.64 (td, *J* = 10.7, 4.3 Hz, 1H), 2.87 (s, 1H), 2.71 – 2.62 (m, 1H), 2.54 (tdd, *J* = 14.3, 5.0, 2.0 Hz, 1H), 2.35 (ddd, *J* = 14.3, 4.4, 2.8 Hz, 1H), 2.25 – 2.17 (m, 1H), 2.15 (d, *J* = 14.9 Hz, 1H), 1.70 (d, *J* = 14.9 Hz, 1H), 1.63 (s, 1H), 1.59 – 1.52 (m, 1H), 1.51 – 1.40 (m, 1H), 1.16 (s, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 200.5, 169.6, 138.6, 121.6, 116.5, 76.2, 71.6, 48.0, 44.9, 40.8, 40.1, 35.9, 31.3, 23.4, 14.4, 11.8. **HRMS** (ESI) Exact mass calculated for $C_{16}H_{24}O_3Na^+$ $[M+Na]^+$: 287.16177, found: 287.16170.



(1*R*,7*R*,8a*R*)-7-((*R*)-But-3-en-2-yl)-7-hydroxy-1,8a-dimethyl-1,3,4,7,8,8a-hexahydronaphthalene-2,6-dione (11*R*-**2.114):** $NaHCO_3$ (138 mg, 1.65 mmol, 8.0 equiv.) and DMP (175 mg, 0.412 mmol, 2.0 equiv.) were added sequentially to a solution of crude 11*R*-**6.7** (54.5 mg, 0.206 mmol, 1.0 equiv.) in CH_2Cl_2 (4.0 mL) at 0°C and the mixture was stirred for 2 h 45 min at this temperature. The mixture was diluted with CH_2Cl_2 and sat. aq. $Na_2S_2O_3$

solution was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organics were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 1:1) to give 11*R*-**2.114** (46.4 mg, 0.177 mmol, 86 % over 2 steps, *dr* 14:1) as a colorless solid.

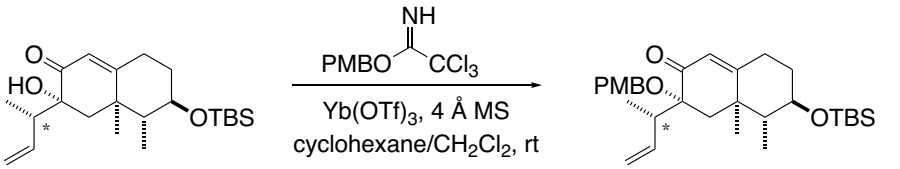
M.p. = 103.0 – 106.7°C. TLC: R_f = 0.47 (SiO_2, pentane/Et_2O 1:2). **Optical rotation**: $[\alpha]_D^{23}$ = –0.4° (c = 0.88, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3469, 2971, 1715, 1672, 1440, 1387, 1238, 1145, 1094, 1008, 885, 836 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.99 (d, *J* = 1.2 Hz, 1H), 5.80 (ddd, *J* = 17.2, 10.4, 7.9 Hz, 1H), 5.14 – 5.01 (m, 2H), 2.90 – 2.80 (m, 1H), 2.84 (s, 1H), 2.77 – 2.63 (m, 3H), 2.62 – 2.49 (m, 2H), 2.19 (d, *J* = 14.9 Hz, 1H), 1.79 (d, *J* = 14.9 Hz, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.11 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 209.3, 200.0, 166.1, 138.3, 122.9, 116.9, 76.0, 52.5, 44.8, 42.2, 40.4, 40.1, 31.6, 23.9, 14.4, 8.2. **HRMS** (ESI) Exact mass calculated for $C_{16}H_{23}O_3^+$ $[M+H]^+$: 263.16417, found: 263.16421; for $C_{16}H_{22}NaO_3^+$ $[M+Na]^+$: 285.14612, found: 285.14613.



(*S*)-2-((2*R*,8*R*,8a*R*)-2-Hydroxy-8,8a-dimethyl-3,7-dioxo-1,2,3,5,6,7,8,8a-octahydro-naphthalen-2-yl)propanal (11*S*-**2.115):** A solution of 11*R*-**2.114** (46.4 mg, 0.177 mmol, 1.0 equiv.), pyridine (57 µL, 0.708 mmol, 4.0 equiv.) and Sudan III (spatula tip) in CH_2Cl_2/MeOH (4.0 mL, 1:1) was cooled to –78°C and O_3 was bubbled through the solution until the red color disappeared (35 sec). The reaction mixture was sequentially purged with O_2 and N_2. PPh_3 (92.9 mg, 0.354 mmol, 2.0 equiv.) was added and the mixture was allowed to warm to rt. After stirring for 1 h, the solvent was removed by evaporation and the residue was purified by flash column chromatography (pentane/Et_2O 1:2) to give 11*S*-**2.115** (41.1 mg, 0.155 mmol, 88 %, *dr* >10:1) as a colorless oil.

TLC: R_f = 0.19 (SiO_2, pentane/Et_2O 1:2). **Optical rotation**: $[\alpha]_D^{23}$ = +13.3° (c = 0.73, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3427, 2977, 1714, 1671, 1441, 1388, 1242, 1151, 1003, 885, 603 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 10.05 (d, *J* = 1.6 Hz, 1H), 5.99 (d, *J* = 1.9 Hz, 1H), 3.90 (s, 1H), 2.93 – 2.80 (m, 1H), 2.80 – 2.70 (m, 2H), 2.64 – 2.50 (m, 2H), 2.43 (q, *J* = 6.7 Hz, 1H), 2.14 (d, *J* = 14.3 Hz, 1H), 1.75 (d, *J* = 14.4 Hz, 1H), 1.23 (s, 3H), 1.13 (d, *J* = 7.2 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 209.0, 206.3, 197.4, 166.4, 122.4,

77.6, 54.5, 49.0, 43.5, 42.6, 40.0, 32.3, 21.9, 9.1, 7.5. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{21}O_4^+$ $[M+H]^+$: 265.14344, found: 265.14337.

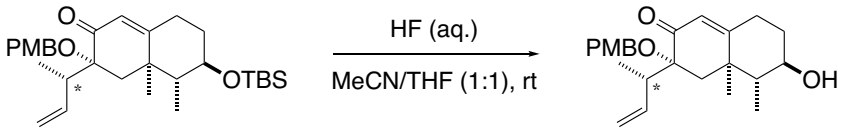


2.80, *dr* 2:1 (11*S*/11*R*) **2.122**, 65 %, *dr* 2:1 (11*S*/11*R*)

(3*R*,4a*R*,5*R*,6*R*)-3-(But-3-en-2-yl)-6-((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)-oxy)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (2.122): To a mixture of 11*S*- and 11*R*-**2.80** (50.0 mg, 0.132 mmol, 1.0 equiv., *dr* 2:1) and 4 Å MS (50.0 mg) in cyclohexane/CH_2Cl_2 (4.5 mL, 2:1) at rt was added $Yb(OTf)_3$ (4.1 mg, 6.6 µmol, 5 mol%), followed by a solution of PMB trichloroacetimidate (0.8 M in CH_2Cl_2, 0.66 mL, 149 mg, 0.528 mmol, 4.0 equiv.) over a period of 105 min. The mixture was stirred for additional 15 min at rt, before it was partitioned between sat. aq. $NaHCO_3$ solution and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was subjected to flash column chromatography (pentane/Et_2O 6:1) to give **2.122** (57.0 mg, 0.086 mmol, 65 %, *dr* 2:1, 75 % purity according to ^{1}H NMR spectrum) as a colorless oil.

TLC: R_f = 0.85 (SiO_2, pentane/Et_2O 3:1). **FTIR** (neat): $\tilde{\nu}$ = 2952, 2857, 1668, 1629, 1614, 1514, 1463, 1385, 1302, 1249, 1173, 1129, 1099, 1072, 1038, 1006, 888, 835, 774 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those from the minor diastereoisomer with [b]) δ = 7.18 – 7.06[a+b] (m, 4H), 6.85 – 6.78[a+b] (m, 4H), 6.03 (ddd, *J* = 17.2, 10.8, 6.6, 1H),[b] 5.82 – 5.78[a+b] (m, 2H), 5.63[a] (ddd, *J* = 17.4, 10.6, 5.6, 1H), 5.19 – 5.02[a+b] (m, 4H), 4.45[b] (d, *J* = 10.8, 1H), 4.37[a] (d, *J* = 11.0, 1H), 4.11[a] (d, *J* = 10.9, 1H), 4.08[b] (d, *J* = 10.7, 1H), 3.79 – 3.76[a+b] (m, 6H), 3.60 – 3.50[a+b] (m, 2H), 3.50 – 3.39[a+b] (m, 2H), 2.50 – 2.39[a+b] (m, 2H), 2.31 – 2.23[a+b] (m, 2H), 2.15[b] (d, *J* = 14.6, 1H), 2.14[a] (d, *J* = 14.7, 1H), 2.08 – 2.00[a+b] (m, 2H), 1.65[b] (d, *J* = 14.7, 1H), 1.60[a] (d, *J* = 14.7, 1H), 1.50 – 1.37[a+b] (m, 2H), 1.32 – 1.22[a+b] (m, 2H), 1.21[a] (s, 3H), 1.20[b] (s, 3H), 1.06[a] (d, *J* = 7.0, 3H), 0.97[a+b] (d, *J* = 6.7, 6H), 0.90[b] (d, *J* = 6.9, 3H), 0.88[b] (s, 9H), 0.88[a] (s, 9H), 0.06[a+b] (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 195.6[b], 195.4[a], 170.1[b], 169.7[a], 158.8[a+b], 139.3[a], 138.5[b], 130.8[a], 130.7[b], 129.1[b] (2C), 128.9[a] (2C), 122.7[a], 122.5[b], 116.0[a], 115.8[b], 113.6[a] (2C), 113.6[b] (2C), 80.0[b], 79.4[a], 71.5[a], 64.5[b], 64.5[a], 64.4[b], 55.2[a+b], 51.8[b], 51.5[a], 40.9[a+b], 39.2[b], 39.1[a], 36.2[b], 36.1[a], 35.1[b], 35.0[a], 31.5[b], 31.5[a], 25.8[a+b] (6C), 21.3[a], 21.1[b], 18.0[a], 15.0[b], 11.1[a], 11.1[b], 10.9[a+b], -4.0[a+b], -4.7[a+b]. **HRMS** (ESI) Exact

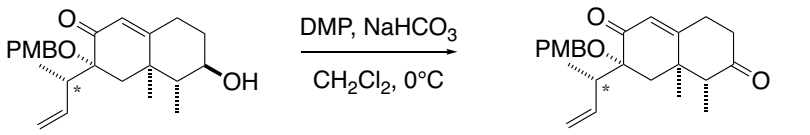
mass calculated for $C_{30}H_{47}O_4Si^+$ $[M+H]^+$: 499.32381, found: 499.32416; for $C_{30}H_{46}NaO_4Si^+$ $[M+Na]^+$: 521.30576, found: 521.30599.



2.122, *dr* 2:1 (11*S*/11*R*) **6.8**, 90 %, *dr* 2:1 (11*S*/11*R*)

(3*R*,4a*R*,5*R*,6*R*)-3-(But-3-en-2-yl)-6-hydroxy-3-((4-methoxybenzyl)oxy)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (6.8): To a solution of **2.122** (75 %, 72.8 mg, 0.109 mmol, 1.0 equiv., *dr* 2:1) in MeCN/THF (4.0 mL, 1:1) was added a solution of HF (48 % in H_2O, 23 µL, 0.545 mmol, 5.0 equiv.). The solution was stirred for 14 h at rt, before sat. aq. $NaHCO_3$ solution was added. The mixture was extracted with Et_2O (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 1:2) to give **6.8** (37.6 mg, 0.098 mmol, 90 %, *dr* 2:1) as a colorless oil.

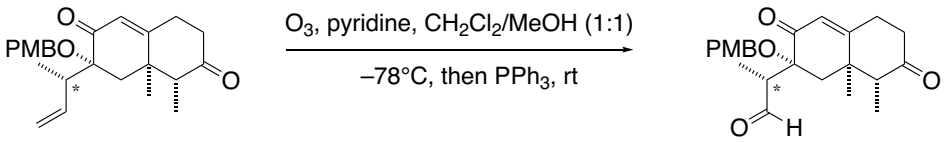
TLC: R_f = 0.25 (SiO_2, pentane/Et_2O 1:2). **FTIR** (neat): $\tilde{\nu}$ = 3437, 2938, 1663, 1514, 1455, 1382, 1302, 1248, 1174, 1034, 914, 885, 820, 689, 571 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those from the minor diastereoisomer with [b]) δ = 7.18 – 7.10[a+b] (m, 4H), 6.86 – 6.78[a+b] (m, 4H), 6.03[b] (ddd, *J* = 17.2, 10.7, 6.5, 1H), 5.85 – 5.80[a+b] (m, 2H), 5.64[a] (ddd, *J* = 17.4, 10.6, 5.6, 1H), 5.21 – 5.13[b] (m, 2H), 5.13 – 5.03[a] (m, 2H), 4.45[b] (d, *J* = 10.7, 1H), 4.36[a] (d, *J* = 10.9, 1H), 4.11[a] (d, *J* = 10.9, 1H), 4.07[b] (d, *J* = 10.6, 1H), 3.78[a] (s, 3H), 3.77[b] (s, 3H), 3.66 – 3.56[a+b] (m, 2H), 3.50 – 3.40[a+b] (m, 2H), 2.54 – 2.45[a+b] (m, 2H), 2.37 – 2.29[a+b] (m, 2H), 2.22 – 2.12[a+b] (m, 4H), 1.64[b] (d, *J* = 14.6, 1H), 1.60[a] (d, *J* = 14.8, 1H), 1.47 – 1.34[a+b] (m, 4H), 1.23 – 1.20[a+b] (m, 6H), 1.09 – 1.03[a+b] (m, 9H), 0.91[b] (d, *J* = 6.8, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those from the minor diastereoisomer with [b]) δ = 195.7[b], 195.5[a], 169.6[b], 169.2[a], 159.0[a+b], 139.4[a], 138.5[b], 130.8[a], 130.8[b], 129.3[b] (2C), 129.1[a] (2C), 123.1[a], 122.9[b], 116.2[a], 116.0[b], 113.8[a] (2C), 113.7[b] (2C), 80.1[b], 79.5[a], 71.0[a], 71.0[b], 64.7[a], 64.6[b], 55.4[a+b], 51.7[b], 51.4[a], 40.9[a+b], 39.4[b], 39.3[a], 35.8[b], 35.7[a], 35.1[b], 35.1[a], 31.6[b], 31.5[a], 21.3[a], 21.2[b], 15.1[b], 11.0[a], 10.7[a], 10.7[b]. **HRMS** (ESI) Exact mass calculated for $C_{24}H_{32}NaO_4^+$ $[M+Na]^+$: 407.21928, found: 407.21934.



6.8, *dr* 2:1 (11*S*/11*R*) **6.9**, 83 %, *dr* 2:1 (11*S*/11*R*)

(1*R*,7*R*,8a*R*)-7-(But-3-en-2-yl)-7-((4-methoxybenzyl)oxy)-1,8a-dimethyl-1,3,4,7,8,8a-hexahydronaphthalene-2,6-dione (6.9): $NaHCO_3$ (65.7 mg, 0.782 mmol, 8.0 equiv.) and DMP (83 mg, 0.196 mmol, 2.0 equiv.) were added sequentially to a solution of **6.8** (37.6 mg, 0.098 mmol, 1.0 equiv.) in CH_2Cl_2 (2.5 mL) at 0°C and the mixture was stirred for 105 min at this temperature. The mixture was diluted with CH_2Cl_2 and sat. aq. $Na_2S_2O_3$ solution was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 2:1) to give **6.9** (31.1 mg, 0.081 mmol, 83 %, *dr* 2:1) as a colorless oil.

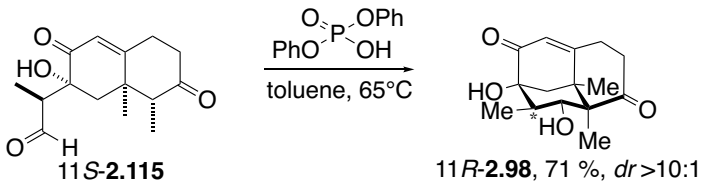
TLC: R_f = 0.24 and 0.31 (SiO_2, pentane/Et_2O 2:1). **FTIR** (neat): $\tilde{\nu}$ = 2972, 1716, 1670, 1614, 1514, 1455, 1376, 1302, 1249, 1175, 1034, 884, 821, 569 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those from the minor diastereoisomer with [b]) δ = 7.16 – 7.09[a+b] (m, 4H), 6.82[a+b] (s, 4H), 6.03[b] (ddd, *J* = 17.2, 10.7, 6.4, 1H), 5.97 – 5.94[a+b] (m, 2H), 5.66[a] (ddd, *J* = 16.7, 10.6, 5.7, 1H), 5.22 – 5.06[a+b] (m, 4H), 4.46[b] (d, *J* = 10.6, 1H), 4.38[a] (d, *J* = 10.9, 1H), 4.09[a] (d, *J* = 10.9, 1H), 4.06[b] (d, *J* = 10.6, 1H), 3.78[a] (s, 3H), 3.77[b] (s, 3H), 3.51 – 3.43[a+b] (m, 2H), 2.87 – 2.77[a+b] (m, 2H), 2.73 – 2.66[a+b] (m, 2H), 2.58 – 2.49[a+b] (m, 4H), 2.44 – 2.36[a+b] (m, 2H), 2.14[b] (d, *J* = 14.6, 1H), 2.13[a] (d, *J* = 14.6, 1H), 1.85[b] (d, *J* = 14.6, 1H), 1.81[a] (d, *J* = 14.6, 1H), 1.16[a] (s, 3H), 1.14[b] (s, 3H), 1.08[a] (d, *J* = 7.0, 3H), 1.03[a+b] (d, *J* = 6.9, 6H), 0.95[b] (d, *J* = 6.8, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those from the minor diastereoisomer with [b]) δ = 209.5[a], 209.4[b], 195.5[b], 195.3[a], 165.7[b], 165.4[a], 159.1[a+b], 139.2[a], 138.2[b], 130.5[a], 130.5[b], 129.3[b] (2C), 129.1[a] (2C), 123.8[a], 123.7[b], 116.6[a], 116.3[b], 113.8[a] (2C), 113.8[b] (2C), 79.8[b], 79.3[a], 64.8[a], 64.7[b], 55.5[b], 55.4[a+b], 55.3[a], 42.5[b], 42.4[a], 40.4[b] (2C), 40.3[a] (2C), 35.0[a+b], 32.5[a+b], 22.0[a], 21.8[b], 15.1[b], 11.0[a], 7.4[a], 7.4[b].



6.9, *dr* 2:1 (11*S*/11*R*) **2.124**, 88 %, *dr* 5:2 (11*R*/11*S*)

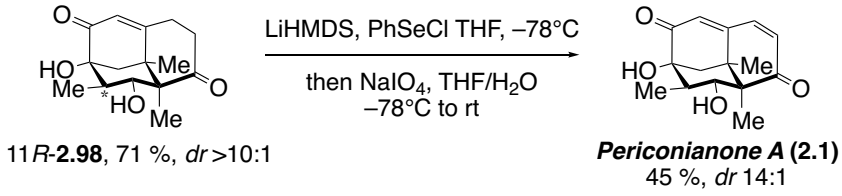
2-((2*R*,8*R*,8a*R*)-2-((4-Methoxybenzyl)oxy)-8,8a-dimethyl-3,7-dioxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)propanal (2.124): A solution of **6.9** (31.1 mg, 81.3 µmol, 1.0 equiv.), pyridine (26 µL, 0.325 mmol, 4.0 equiv.) and Sudan III (spatula tip) in CH_2Cl_2/MeOH (3.0 mL, 1:1) was cooled to –78°C and O_3 was bubbled through the solution until the red color disappeared (<1 min). The reaction mixture was sequentially purged with O_2 and N_2. PPh_3 (42.6 mg, 0.163 mmol, 2.0 equiv.) was added and the mixture was allowed to warm up to rt. After stirring for 45 min, the solvent was removed by evaporation and the residue was subjected to flash column chromatography (pentane/ Et_2O 1:1) to give **2.124** (27.5 mg, 71.5 µmol, 88 %, *dr* 5:2) as colorless oil.

TLC: R_f = 0.17 (SiO_2, pentane/Et_2O 1:1). **FTIR** (neat): $\tilde{\nu}$ = 2942, 1716, 1670, 1614, 1515, 1442, 1248, 1176, 1033, 884, 822 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those from the minor diastereoisomer with [b]) δ = 9.98[b] (d, *J* = 1.6, 1H), 9.66[a] (s, 1H), 7.17 – 7.08[a+b] (m, 4H), 6.87 – 6.76[a+b] (m, 4H), 6.04[a] (d, *J* = 1.7, 1H), 5.99[b] (d, *J* = 1.7, 1H), 4.61[b] (d, *J* = 10.7, 1H), 4.29[a] (d, *J* = 10.7, 1H), 4.21[b] (d, *J* = 10.8, 1H), 4.10[a] (d, *J* = 10.7, 1H), 3.78[a+b] (s, 6H), 3.73[a] (q, *J* = 7.4, 1H), 3.65[b] (ddd, *J* = 13.3, 6.5, 1.2, 1H), 2.89 – 2.79[a+b] (m, 2H), 2.77 – 2.68[a+b] (m, 2H), 2.59 – 2.52[a+b] (m, 4H), 2.42[a+b] (q, *J* = 6.7, 2H), 2.18[a] (d, *J* = 14.6, 1H), 2.13[b] (d, *J* = 14.6, 1H), 2.02[b] (d, *J* = 14.6, 1H), 1.81[a] (d, *J* = 14.5, 1H), 1.19[a] (d, *J* = 7.5, 3H), 1.17[a+b] (s, 6H), 1.04 – 0.99[a+b] (m, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$, signals from the major diastereoisomer are marked with [a], those from the minor diastereoisomer with [b]) δ = 209.1[a], 208.8[b], 204.6[b], 202.7[a], 195.2[a], 193.7[b], 166.7[b], 166.3[a], 159.3[b], 159.3[a], 130.0[b], 129.7[a], 129.4[b] (2C), 129.2[a] (2C), 123.0[a], 122.9[b], 113.9[b] (2C), 113.9[a] (2C), 80.4[b], 77.9[a], 65.8[b], 65.4[a], 55.4[a+b], 55.4[b], 55.3[a], 45.9[a], 44.7[b], 42.6[a], 42.5[b], 41.9[a], 41.8[b], 40.3[a], 40.3[b], 32.6[a], 32.6[b], 22.2[a], 21.9[b], 9.9[b], 7.4[a], 7.0[a+b]. **HRMS** (ESI) Exact mass calculated for $C_{23}H_{28}NaO_5^+$ $[M+Na]^+$: 407.18290, found: 407.18279.



(1*R*,7*R*,8a*S*,9*R*,10*R*)-7,10-Dihydroxy-1,8a,9-trimethyl-1,3,4,7,8,8a-hexahydro-1,7-ethanonaphthalene-2,6-dione (11*R*-**2.98):** To a solution of 11*S*-**2.115** (33.8 mg, 0.128 mmol, 1.0 equiv.) in toluene (5.0 mL) was added diphenyl phosphate (16.0 mg, 64 µmol, 0.5 equiv.) and the mixture was heated at 65°C for 100 min. The yellow solution was partitioned between sat. aq. $NaHCO_3$ and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (2 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/EtOAc 1:1) to give 11*R*-**2.98** (23.9 mg, 90 µmol, 71 %, *dr* >10:1) as a colorless solid.

M.p. = 149.4 – 154.8°C. TLC: R_f = 0.19 (SiO_2, pentane/EtOAc 1:1). **Optical rotation**: $[\alpha]_D^{23}$ = –79.8° (c = 0.24, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3464, 2963, 1704, 1676, 1450, 1388, 1282, 1216, 1148, 1097, 1059, 1038, 760 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.15 (d, *J* = 1.5 Hz, 1H), 4.05 (s, 1H), 3.84 (dd, *J* = 10.4, 5.9 Hz, 1H), 2.93 (tdd, *J* = 12.2, 7.8, 1.6 Hz, 1H), 2.81 (ddd, *J* = 16.5, 11.8, 8.1 Hz, 1H), 2.69 (dd, *J* = 15.8, 7.2 Hz, 1H), 2.60 (dd, *J* = 12.5, 8.6 Hz, 1H), 2.08 (d, *J* = 13.5 Hz, 1H), 1.90 (d, *J* = 13.5 Hz, 1H), 1.80 – 1.72 (m, 1H), 1.70 (d, *J* = 6.4 Hz, 1H), 1.20 (s, 3H), 1.14 (s, 3H), 0.95 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 210.4, 199.6, 167.7, 123.8, 76.2, 75.7, 58.6, 43.5, 41.9, 41.4, 38.1, 30.1, 23.3, 11.5, 8.4. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{21}O_4^+$ $[M+H]^+$: 265.14344, found: 265.14352.

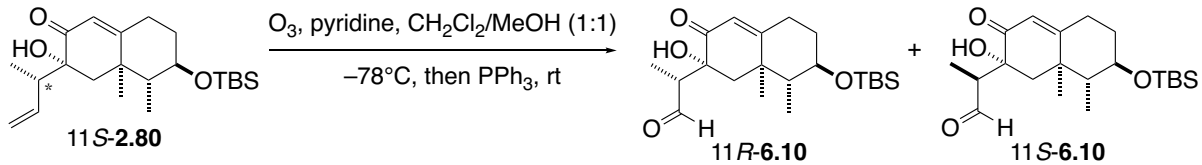


Periconianone A (2.1): To a stirred solution of 11*R*-**2.98** (4.0 mg, 15 µmol, 1.0 equiv.) in THF (0.4 mL) at –78°C was added dropwise a solution of LiHMDS (1.0 M in THF, 60 µL, 60 µmol, 4.0 equiv.). The reaction mixture was stirred at –78°C for 1 h and then PhSeCl (5.8 mg, 30 µmol, 2.0 equiv.) in THF (0.15 mL) was added dropwise. The mixture was stirred for another 2.5 h at –78°C and then quenched by addition of $NaIO_4$ (19.4 mg, 91 µmol, 6.0 equiv.) in H_2O (0.15 mL). After warming to rt, the mixture was stirred for 1.5 h, before additional $NaIO_4$ (19.4 mg, 91 µmol, 6.0 equiv.) in H_2O (0.15 mL) was added at rt. To the

slurry was added sat. aq. Na_2CO_3 solution and the mixture was extracted with EtOAc (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/EtOAc 1:1) to give periconianone A (**2.1**) (1.8 mg, 7 µmol, 45 %, *dr* 14:1) as colorless crystals.

M.p. = 169.8 – 172.4°C. TLC: R_f = 0.18 (SiO_2, pentane/EtOAc 1:1). **Optical rotation**: $[\alpha]_D^{23}$ = +243.0° (c = 0.72, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3459, 2928, 1668, 1610, 1464, 1386, 1280, 1207, 1145, 1118, 1063, 1035, 945, 908, 884, 758 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$, 310 K) δ = 7.28 (d, *J* = 10.1 Hz, 1H), 6.14 (s, 1H), 6.08 (d, *J* = 10.1 Hz, 1H), 3.99 (s, 1H), 3.54 (d, *J* = 10.3 Hz, 1H), 2.22 (d, *J* = 14.0 Hz, 1H), 1.94 – 1.87 (m, 1H), 1.87 (d, *J* = 13.7 Hz, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 0.94 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 200.7, 199.0, 162.6, 142.3, 130.1, 122.7, 75.9, 74.0, 55.8, 44.9, 44.8, 40.0, 24.6, 12.0, 8.1. **^{1}H NMR** (500 MHz, DMSO-d_6, 308 K) δ = 7.45 (d, *J* = 10.2 Hz, 1H), 6.12 (s, 1H), 5.94 (d, *J* = 10.1 Hz, 1H), 5.07 (s, 1H), 4.83 (d, *J* = 7.2 Hz, 1H), 3.38 – 3.31 (m, 1H), 1.96 (d, *J* = 13.8 Hz, 1H), 1.73 (d, *J* = 13.8 Hz, 1H), 1.60 (dq, *J* = 10.1, 6.7 Hz, 1H), 1.08 (s, 3H), 1.06 (s, 3H), 0.76 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ = 199.9, 198.7, 161.4, 142.3, 128.8, 123.4, 75.7, 72.8, 56.0, 44.9, 44.9, 40.2, 23.3, 12.2, 8.0. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{19}O_4^+$ $[M+H]^+$: 263.12779, found: 263.12812; for $C_{15}H_{18}NaO_4^+$ $[M+Na]^+$: 285.10973, found: 285.11000.

6.4 Microsphaeropsisin B and C, Periconianone C[218]



83 %, *dr* 2:1 (11*R*/11*S*)

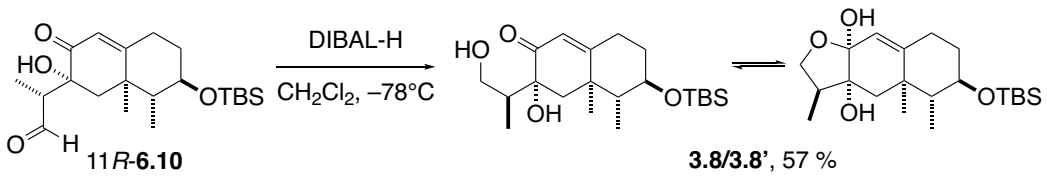
A solution of 11*S*-**2.80** (24.0 mg, 63.4 µmol, 1.0 equiv., *dr* 2:1), pyridine (20 µL, 0.254 mmol, 4.0 equiv.) and Sudan III (spatula tip) in CH_2Cl_2/MeOH (5.0 mL, 1:1) was cooled to –78°C and O_3 was bubbled through the solution until the red color disappeared (25 sec). The reaction mixture was sequentially purged with O_2 and N_2. PPh_3 (33.3 mg, 0.127 mmol, 2.0 equiv.) was added and the mixture was allowed to warm to rt. After stirring for 1 h, the solvent was removed by evaporation and the residue was purified by flash column chromatography (pentane/Et_2O 1:1) to give 11*R*- and 11*S*-**6.10** (20.1 mg, 53 µmol, 83 %, *dr* 2:1) as a colorless solid. For analytical purposes, purification by additional flash column chromatography (pentane/Et_2O 2:1) gave access to diastereomerically pure 11*R*- and 11*S*-**6.10**.

(*R*)-2-((2*R*,7*R*,8*R*,8a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)propanal (11*R*-**6.10):**

M.p. = 145.5 – 147.8 °C. TLC: R_f = 0.49 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{26}$ = +15.6° (c = 0.66, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3426, 2951, 2930, 2857, 1719, 1669, 1463, 1387, 1250, 1099, 1072, 887, 835, 774, 673 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.79 (d, *J* = 1.0, 1H), 5.83 (d, *J* = 1.6, 1H), 4.06 (d, *J* = 1.8, 1H), 3.59 (ddd, *J* = 10.9, 9.8, 4.5, 1H), 2.54 – 2.46 (m, 2H), 2.32 (ddd, *J* = 14.5, 4.4, 2.7, 1H), 2.10 – 2.04 (m, 1H), 2.00 (d, *J* = 14.5, 1H), 1.92 (dd, *J* = 14.5, 1.9, 1H), 1.51 – 1.38 (m, 2H), 1.28 (s, 3H), 1.17 (d, *J* = 7.3, 3H), 1.01 (d, *J* = 6.7, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 206.6, 197.1, 171.3, 121.3, 79.2, 71.7, 50.7, 50.6, 44.7, 40.3, 36.2, 31.7, 26.0 (3C), 21.7, 18.2, 11.5, 10.4, -3.9, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{21}H_{37}O_4Si^+$ $[M+H]^+$: 381.24556, found: 381.24557.

(*S*)-2-((2*R*,7*R*,8*R*,8a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-8,8a-dimethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)propanal (11*S*-**6.10):**

M.p. = 133.9 – 137.9 °C. TLC: R_f = 0.59 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{26}$ = +23.6° (c = 0.15, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3443, 2952, 2930, 2857, 1722, 1670, 1463, 1251, 1100, 1073, 887, 835, 774, 673 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 10.04 (d, *J* = 1.9, 1H), 5.84 (d, *J* = 1.6, 1H), 3.69 (d, *J* = 1.8, 1H), 3.59 (ddd, *J* = 11.0, 9.9, 4.6, 1H), 2.73 (qd, *J* = 7.1, 1.9, 1H), 2.50 (tdd, *J* = 14.6, 5.1, 1.8, 1H), 2.33 (ddd, *J* = 14.4, 4.5, 2.7, 1H), 2.12 (d, *J* = 14.5, 1H), 2.09 – 2.03 (m, 1H), 1.61 (dd, *J* = 14.6, 1.8, 1H), 1.44 (dddd, *J* = 14.6, 12.6, 11.0, 4.5, 1H), 1.36 – 1.27 (m, 1H), 1.28 (s, 3H), 1.11 (d, *J* = 7.2, 3H), 1.01 (d, *J* = 6.7, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 206.4, 197.8, 170.9, 121.1, 77.9, 71.6, 50.8, 49.6, 44.1, 40.0, 36.2, 31.7, 26.0 (3C), 21.4, 18.2, 11.5, 9.2, -3.8, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{21}H_{37}O_4Si^+$ $[M+H]^+$: 381.24556, found: 381.24559.

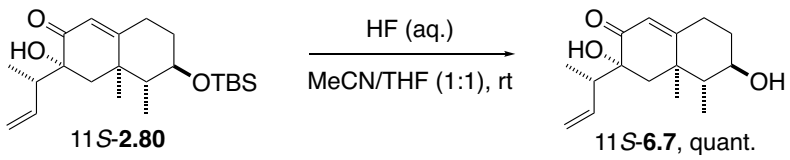


11*R*-**6.10** **3.8/3.8'**, 57 %

(3*S*,3a*R*,4a*R*,5*R*,6*R*,9a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-3,4a,5-trimethyl-2,3,4,4a,5,6,7,8-octahydronaphtho[2,3-*b*]furan-3a,9a-diol (3.8) and (3*R*,4a*R*,5*R*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-3-((*S*)-1-hydroxypropan-2-yl)-4a,5-dimethyl-

4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (3.8'): DIBAL-H (1.2 M in toluene, 66 µL, 79 µmol, 2.5 equiv.) was added dropwise to a solution of 11*R*-**6.10** (12 mg, 32 µmol, 1.0 equiv.) in CH_2Cl_2 (0.6 mL) at –78°C and the mixture was stirred for 30 min at this temperature. MeOH and sat. aq. Rochelle's solution were added and the layers were separated after the mixture warmed up to rt. The aqueous layer was extracted with CH_2Cl_2 (3 x), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 2:3) to give **3.8/3.8'** (6.9 mg, 18 µmol, 57 %) as a colorless solid.

M.p. = 107.5 – 109.1°C. TLC: R_f = 0.33 (SiO_2, pentane/Et_2O 2:3). **FTIR** (neat): $\tilde{\nu}$ = 3391, 2950, 2930, 2883, 2857, 1660, 1462, 1251, 1068, 1006, 890, 835, 773, 677 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$, signals from the closed form are marked with [a], those from the open form with [b]; ratio a/b = 1:2.4) δ = 5.83[b] (d, *J* = 1.9, 1H), 5.33[a] (d, *J* = 1.9, 1H), 4.07[a] (t, *J* = 8.6, 1H), 3.93[b] (dd, *J* = 11.3, 3.8, 1H), 3.69[b] (s, 1H), 3.68 – 3.64[b] (m, 1H), 3.59[b] (td, *J* = 11.0, 4.5, 1H), 3.52[a] (td, *J* = 10.5, 4.6, 1H), 3.33[a] (dd, *J* = 10.5, 8.6, 1H), 2.77[b] (d, *J* = 8.0, 1H), 2.65[a] (s, 1H), 2.55 – 2.44[a+b] (m, 2H), 2.38[b] (d, *J* = 15.0, 1H), 2.33 – 2.25[a+b] (m, 3H), 2.14 – 2.03[a+b] (m, 3H), 1.97 – 1.93[a] (m, 1H), 1.90[a] (d, *J* = 14.2, 1H), 1.72[b] (d, *J* = 15.0, 1H), 1.57 – 1.53[b] (m, 1H), 1.50 – 1.38[a+b] (m, 2H), 1.22 – 1.18[a] (m, 2H), 1.16[a+b] (s, 6H), 1.08[b] (d, *J* = 6.7, 3H), 1.01[a] (d, *J* = 6.9, 3H), 0.97[a] (d, *J* = 6.8, 3H), 0.91[b] (d, *J* = 7.1, 3H), 0.89[b] (s, 9H), 0.87[a] (s, 9H), 0.08[b] (s, 3H), 0.07[b] (s, 3H), 0.05[a] (s, 3H), 0.04[a] (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, signals from the closed form are marked with [a], those from the open form with [b]) δ = 200.9[b], 170.5[b], 147.4[a], 120.7[b], 118.8[a], 99.9[a], 77.4[b], 77.3[a], 72.4[b], 72.2[a], 71.0[a], 64.5[b], 51.6[a], 48.1[b], 42.7[a], 42.4[b], 40.7[b], 40.6[b], 39.0[a], 38.5[a], 36.5[a], 36.3[b], 31.3[b], 30.6[a], 26.0[a+b] (6C), 24.0[a], 20.5[a], 18.2[b], 18.2[a], 12.4[b], 11.9[b], 11.5[a], 9.4[a], -3.8[a], -3.9[b], -4.5[b], -4.5[a]. **HRMS** (ESI) Exact mass calculated for $C_{21}H_{39}O_4Si^+$ $[M+H]^+$: 383.26121, found: 383.26095.

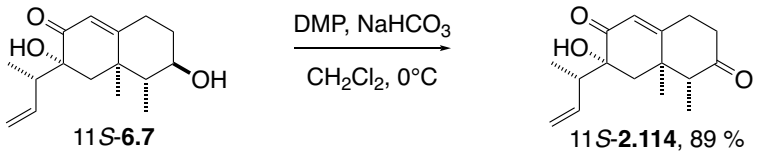


11*S*-**2.80** 11*S*-**6.7**, quant.

(3*R*,4a*R*,5*R*,6*R*)-3-((*S*)-But-3-en-2-yl)-3,6-dihydroxy-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (11*S*-**6.7):** To a solution of 11*S*-**2.80** (165 mg, 0.436 mmol, 1.0 equiv.) in MeCN/THF (1:1, 7.0 mL) was added a solution of HF (48 % in H_2O, 0.184 mL, 4.36 mmol, 10 equiv.). The mixture was stirred for 60 h at rt, before it was quenched with sat.

aq. $NaHCO_3$ solution and extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Crude 11*S*-**6.7** (114 mg, 0.431 mmol, 99 %, *dr* 15:1) was obtained as a colorless oil and used without further purification in the next step. For analytical purposes, 11*S*-**6.7** was purified by flash column chromatography (pentane/Et_2O 1:2).

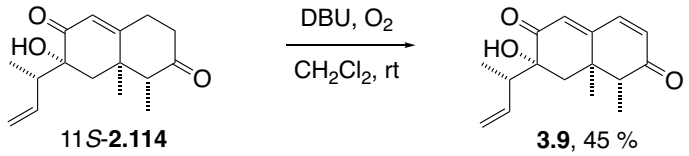
TLC: R_f = 0.11 (SiO_2, pentane/Et_2O 1:1). **Optical rotation:** $[\alpha]_D^{25}$ = +6.1° (c = 0.49, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3413, 2971, 2938, 2880, 1656, 1455, 1384, 1242, 1127, 1028, 915, 884, 687, 580 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.84 (d, *J* = 1.9, 1H), 5.88 – 5.79 (m, 1H), 5.15 – 5.05 (m, 2H), 3.63 (td, *J* = 10.6, 4.5, 1H), 3.05 (d, *J* = 0.9, 1H), 2.64 – 2.57 (m, 1H), 2.54 (tdd, *J* = 14.4, 4.6, 2.0, 1H), 2.35 (ddd, *J* = 14.3, 4.5, 2.8, 1H), 2.22 – 2.16 (m, 1H), 2.18 (d, *J* = 15.1, 1H), 1.71 (d, *J* = 14.8, 1H), 1.64 – 1.57 (m, 2H), 1.52 – 1.40 (m, 1H), 1.14 (s, 3H), 1.11 (d, *J* = 6.7, 3H), 0.95 (d, *J* = 6.9, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 200.9, 170.0, 139.1, 121.6, 117.3, 75.9, 71.6, 48.0, 45.3, 41.8, 40.2, 35.8, 31.3, 23.5, 14.2, 11.8. **HRMS** (ESI) Exact mass calculated for $C_{16}H_{24}O_3Na^+$ $[M+Na]^+$: 287.16177, found: 287.16174.



(1*R*,7*R*,8a*R*)-7-((*S*)-But-3-en-2-yl)-7-hydroxy-1,8a-dimethyl-1,3,4,7,8,8a-hexahydro-naphthalene-2,6-dione (11*S*-**2.114):** $NaHCO_3$ (290 mg, 3.46 mmol, 8.0 equiv.) and DMP (458 mg, 1.08 mmol, 2.5 equiv.) were added sequentially to a solution of crude 11*S*-**6.7** (114 mg, 0.431 mmol, 1.0 equiv.) in CH_2Cl_2 (6.0 mL) at 0°C and the mixture was stirred for 2 h 30 min at this temperature, before it was diluted with CH_2Cl_2 and sat. aq. $Na_2S_2O_3$ solution was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 1:1) to give 11*S*-**2.114** (103 mg, 0.393 mmol, 89 % over 2 steps) as a colorless solid.

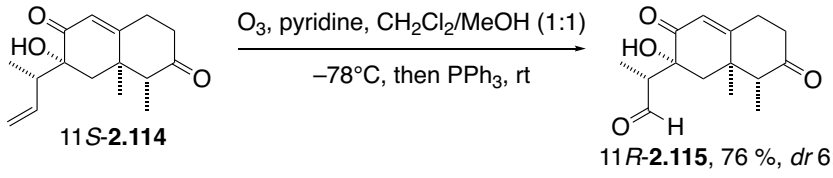
M.p. = 71.1 – 72.0°C. TLC: R_f = 0.31 (SiO_2, pentane/Et_2O 1:1). **Optical rotation:** $[\alpha]_D^{25}$ = –4.0° (c = 0.33, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3470, 2972, 1714, 1670, 1454, 1375, 1238, 1134, 1027, 920, 883, 677, 566 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.99 (d, *J* = 1.2, 1H), 5.87 (ddd, *J* = 17.3, 10.4, 8.3, 1H), 5.15 (ddd, *J* = 10.5, 1.7, 0.8, 1H), 5.05 (ddd, *J* = 17.3, 1.7, 1.0, 1H), 3.11 (d, *J* = 0.8, 1H), 2.89 – 2.81 (m, 1H), 2.76 – 2.53 (m, 5H), 2.27 (d, *J* = 14.0, 1H), 1.77 (d, *J* = 14.8, 1H), 1.10 (d, *J* = 6.6, 3H), 1.08 (s, 3H), 0.98 (d, *J* = 6.9, 3H). **^{13}C NMR** (101

MHz, $CDCl_3$) δ = 209.5, 200.7, 166.3, 138.9, 122.6, 117.5, 75.9, 52.3, 45.5, 42.4, 41.3, 40.1, 31.5, 24.4, 14.5, 8.4. **HRMS** (ESI) Exact mass calculated for $C_{16}H_{23}O_3^+$ $[M+Na]^+$: 285.14612, found: 285.14605.



(1*R*,7*R*,8a*R*)-7-((*S*)-But-3-en-2-yl)-7-hydroxy-1,8a-dimethyl-1,7,8,8a-tetrahydronaphthalene-2,6-dione (3.9): DBU (17 µL, 0.12 mmol, 3.0 equiv.) was added to a solution of 11*S*-**2.114** (10 mg, 38 µmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) at rt and the mixture was stirred under an O_2 atmosphere for 17 h. The reaction mixture was then diluted with sat. aq. NH_4Cl solution and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 1:1) to give **3.9** (5.0 mg, 89 % purity according to ^{1}H NMR spectrum, 17 µmol, 45 %) as a yellowish oil.

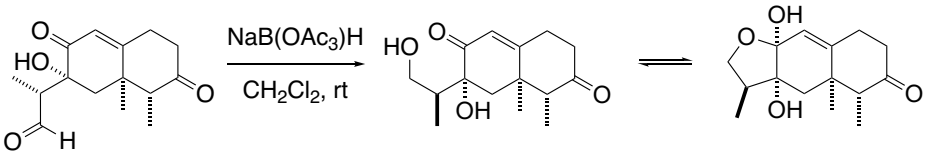
TLC: R_f = 0.43 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{25}$ = +62.8° (c = 0.25, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3470, 2977, 2934, 1714, 1665, 1454, 1389, 1235, 1127, 1078, 919, 890, 834 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.01 (dd, *J* = 10.0, 0.7, 1H), 6.23 (d, *J* = 9.8, 1H), 6.12 (s, 1H), 5.67 (ddd, *J* = 17.1, 10.5, 7.5, 1H), 5.13 – 5.05 (m, 2H), 2.75 – 2.55 (m, 2H), 2.45 (d, *J* = 1.9, 1H), 2.07 (d, *J* = 14.5, 1H), 2.00 (dd, *J* = 14.5, 1.3, 1H), 1.24 (s, 3H), 1.18 (d, *J* = 6.8, 3H), 1.09 (d, *J* = 6.9, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 201.1, 199.8, 160.3, 141.8, 138.2, 132.5, 128.1, 118.0, 75.7, 52.1, 47.2, 40.5, 40.1, 23.1, 13.0, 7.5. **HRMS** (EI) Exact mass calculated for $C_{16}H_{20}O_3$ $[M]^+$: 260.14070, found: 260.14107.



(*R*)-2-((2*R*,8*R*,8a*R*)-2-Hydroxy-8,8a-dimethyl-3,7-dioxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-yl)propanal (11*R*-**2.115):** A solution of 11*S*-**2.114** (48.0 mg, 0.183 mmol, 1.0 equiv.), pyridine (59 µL, 0.73 mmol, 4.0 equiv.) and Sudan III (spatula tip) in

CH_2Cl_2/MeOH (5.0 mL, 1:1) was cooled to –78°C and O_3 was bubbled through the solution until the red color disappeared (40 sec). The reaction mixture was sequentially purged with O_2 and N_2. PPh_3 (96.0 mg, 0.366 mmol, 2.0 equiv.) was added and the mixture was allowed to warm to rt. After stirring for 1 h, the solvent was removed by evaporation and the residue was purified by flash column chromatography (pentane/Et_2O 1:2) to give 11*R*-**2.115** (36.7 mg, 0.139 mmol, 76 %, *dr* 6:1) as a colorless solid.

M.p. = 158.2 – 160.0 °C. TLC: R_f = 0.18 (SiO_2, pentane/Et_2O 1:2). **Optical rotation**: $[\alpha]_D^{26}$ = +29.8° (c = 0.23, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3424, 2977, 1715, 1671, 1440, 1387, 1242, 1154, 1030, 886 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 9.78 (d, *J* = 1.3, 1H), 6.00 (d, *J* = 1.9, 1H), 4.06 (s, 1H), 2.87 (dddd, *J* = 14.9, 12.9, 7.0, 1.9, 1H), 2.77 – 2.70 (m, 1H), 2.61 – 2.51 (m, 4H), 2.10 (d, *J* = 14.4, 1H), 2.01 (d, *J* = 14.5, 1H), 1.22 (d, *J* = 7.3, 3H), 1.22 (s, 3H), 1.08 (d, *J* = 6.7, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 209.0, 206.4, 196.8, 166.7, 122.4, 78.3, 54.1, 50.7, 43.6, 42.9, 40.2, 32.3, 22.6, 10.2, 7.7. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{21}O_4^+$ $[M+H]^+$: 265.14344, found: 265.14360.



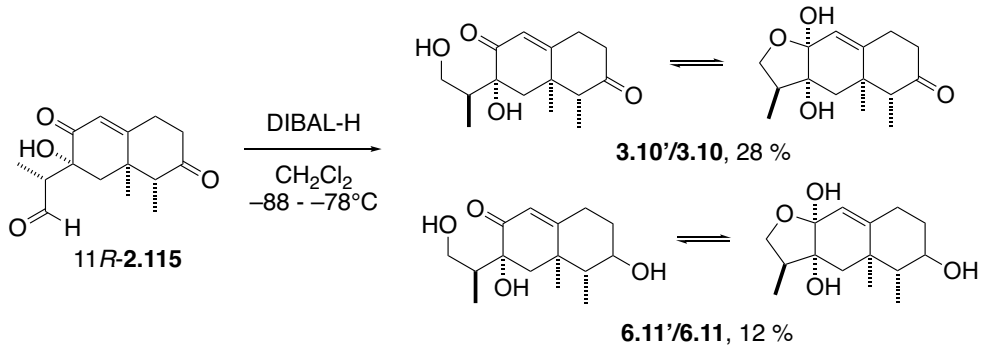
11*R*-**2.115** **3.10/3.10'**, 63 %

(3*S*,3a*R*,4a*R*,5*R*,9a*S*)-3a,9a-Dihydroxy-3,4a,5-trimethyl-2,3,3a,4a,5,7,8,9a-octahydro-naphtho[2,3-*b*]furan-6(4*H*)-one (3.10) and (1*R*,7*R*,8a*R*)-7-hydroxy-7-((*S*)-1-hydroxy-propan-2-yl)-1,8a-dimethyl-1,3,4,7,8,8a-hexahydronaphthalene-2,6-dione (3.10'): $NaBH(OAc)_3$ (153 mg, 0.722 mmol, 3.0 equiv.) was added to a solution of 11*R*-**2.115** (63.5 mg, 0.240 mmol, 1.0 equiv.) in CH_2Cl_2 (8.0 mL) and the mixture was stirred for 2 h at rt. Sat. aq. NH_4Cl solution was added and stirring was continued 30 min before the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 1:10) to give **3.10/3.10'** (40.0 mg, 0.150 mmol, 63 %) as a colorless oil.

TLC: R_f = 0.40 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{25}$ = +21.9° (c = 1.4, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3417, 2968, 2942, 2881, 1711, 1670, 1442, 1385, 1291, 1153, 1013, 878, 731, 633 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$, signals from the closed form are marked with [a], those from the open

form with [b]; ratio a/b = 1.8:1) δ = 6.01[b] (d, *J* =1.9, 1H), 5.53[a] (d, *J* = 2.0, 1H), 4.14[a] (t, *J* = 8.7, 1H), 3.88[b] (dd, *J* = 11.1, 4.3, 1H), 3.76 – 3.70[b] (m, 1H), 3.68[a] (s, 1H), 3.40[a] (dd, *J* = 10.3, 8.6, 1H), 2.86[b] (dddd, *J* = 14.9, 13.1, 6.4, 2.0, 1H), 2.73 – 2.64[b] (m, 2H), 2.71[b] (s, 1H), 2.58[b] (dd, *J* = 6.5, 2.9, 1H), 2.57 – 2.50[a+b] (m, 3H), 2.47 – 2.43[a+b] (m, 4H), 2.40[b] (s, 1H), 2.36[a] (s, 1H), 2.33[a] (q, *J* = 6.9, 1H), 2.17 – 2.13[b] (m, 1H), 1.89[a] (d, *J* = 14.2, 1H), 1.84[b] (d, *J* = 14.9, 1H), 1.41[a] (dd, *J* = 14.2, 2.0, 1H), 1.15[b] (d, *J* = 6.7, 3H), 1.13[b] (s, 3H), 1.12[a] (s, 3H), 1.03[a] (d, *J* = 6.9, 6H), 0.94[b] (d, *J* = 6.9, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, signals from the closed form are marked with [a], those from the open form with [b]) δ = 211.1[a], 209.1[b], 200.4[b], 166.1[b], 144.3[a], 122.4[b], 120.7[a], 99.7[a], 77.3[a] (according to HMBC), 76.7[b], 71.3[a], 64.6[b], 55.8[a], 52.6[b], 42.7[b], 42.4[a], 42.1[a], 41.7[b], 41.1[a], 40.8[b], 40.3[b], 38.4[a], 31.9[a], 31.7[b], 24.4[b], 21.1[a], 11.9[b], 9.5[a], 8.3[b], 7.6[a]. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{23}O_4^+$ $[M+H]^+$: 267.15909, found: 267.15906.

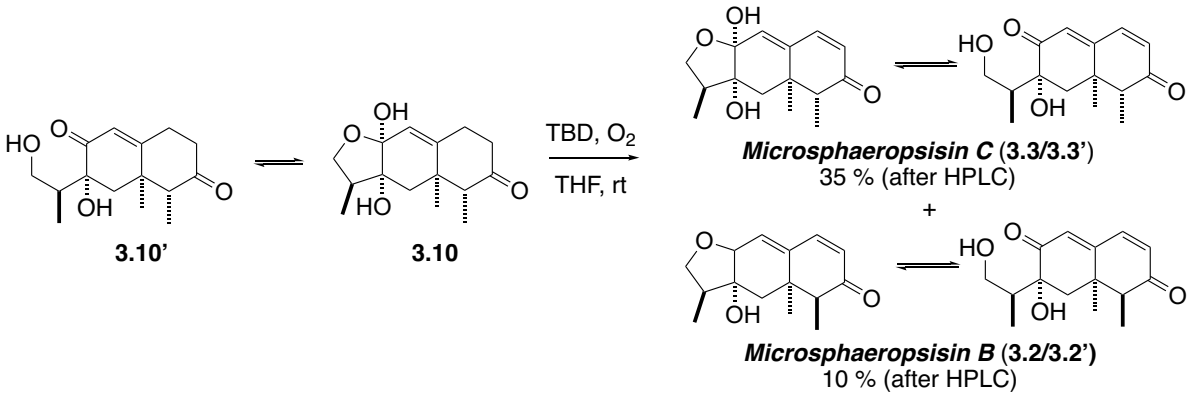
or



Stock solution: DIBAL-H (1.2 M in toluene, 0.28 mL, 0.34 mmol) was added to CH_2Cl_2 (2.0 mL) and the mixture was stirred for 5 min at rt. The prepared stock solution (0.23 mL, 34 µmol, 1.5 equiv.) was added slowly along the wall of the reaction vessel to a mixture of 11*R*-**2.115** (6.0 mg, 23 µmol, 1.0 equiv.) in CH_2Cl_2 (0.6 mL) at –88°C and stirred at –88 - –78°C for 50 min. MeOH and sat. aq. Rochelle's solution were added and the layers were separated after the mixture warmed up to rt. The aqueous layer was extracted with CH_2Cl_2 (3 x), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 1:10) to give **3.10/3.10'** (1.7 mg, 6.4 µmol, 28 %) as a colorless oil, SM (1.0 mg, 68 % pure, 2.6 µmol, 11 %) as a slightly yellow solid as well as **6.11/6.11'** (0.9 mg, 83 % pure, 2.8 µmol, 12 %) as a colorless solid.

(3*S*,3a*R*,4a*R*,5*R*,9a*S*)-3,4a,5-Trimethyl-2,3,4,4a,5,6,7,8-octahydronaphtho[2,3-*b*]furan-3a,6,9a-triol (6.11) and (3*R*,4a*R*,5*R*)-3,6-dihydroxy-3-((*S*)-1-hydroxypropan-2-yl)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (6.11'): M.p. = 130.9 – 131.7°C. TLC: R_f = 0.30 (SiO_2, Et_2O). **FTIR** (neat): $\tilde{\nu}$ = 3413, 2963, 2937, 2880, 1654, 1457, 1373,

1244, 1032, 1007, 945, 731, 646 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$, signals from the closed form are marked with [a], those from the open form with [b]; ratio a/b = 1:2.9) δ = 5.88[b] (d, *J* = 1.8, 1H), 5.40[a] (d, *J* = 1.8, 1H), 4.08[a] (t, *J* = 8.6, 1H), 3.94[b] (s, 1H), 3.92[b] (dd, *J* = 11.1, 4.1, 1H), 3.86[a] (s, 1H), 3.69[a] (s, 1H), 3.66 – 3.61[b] (m, 1H), 3.66[b] (s, 1H), 3.32[a] (dd, *J* = 10.5, 8.5, 1H), 2.96 – 2.88[b] (m, 1H), 2.79[a] (s, 1H), 2.74 – 2.64[a] (m, 1H), 2.73[b] (s, 1H), 2.47 – 2.43[a] (m, 1H), 2.35[b] (d, *J* = 15.0, 1H), 2.18[b] (dt, *J* = 13.4, 3.5, 1H), 2.12 – 2.06[b] (m, 1H), 2.01 – 1.95[a+b] (m, 3H), 1.90[a] (d, *J* = 14.2, 1H), 1.77 – 1.71[b] (m, 2H), 1.70 – 1.68[a] (m, 1H), 1.68[b] (d, *J* = 15.0, 1H), 1.58[b] (s, 1H), 1.45[a] (s, 1H), 1.41[a] (s, 3H), 1.38[b] (s, 3H), 1.34 – 1.31[a] (m, 1H), 1.19[b] (d, *J* = 7.1, 3H), 1.13[a] (d, *J* = 14.2, 1H), 1.10[a] (d, *J* = 7.2, 3H), 1.01[a] (d, *J* = 7.0, 3H), 0.90[b] (d, *J* = 7.0, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, signals from the closed form are marked with [a], those from the open form with [b]) δ = 201.0[b], 172.7[b], 148.7[a], 120.3[b], 118.7[a], 99.9[a], 77.5[b] (according to HMBC), 77.2[a] (according to HMBC), 72.3[a], 71.0[b], 70.9[a], 64.3[b], 47.6[a], 44.1[b], 42.9[a], 42.6[b], 41.0[b], 40.7[b], 39.0[a], 38.5[a], 35.0[b], 34.6[a], 27.9[b], 26.9[a], 26.1[b], 22.3[a], 12.5[b], 12.3[a], 11.8[b], 9.4[a]. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{24}O_4Na^+$ $[M+Na]^+$: 291.15668, found: 291.15657.



Microsphaeropsisin C (3.3/3.3') and microsphaeropsisin B (3.2/3.2'): To a solution of **3.10/3.10'** (19.0 mg, 71.3 µmol, 1.0 equiv.) in THF (2.0 ml, distilled prior to use) was added TBD (29.9 mg, 0.214 mmol, 3.0 equiv.) and the mixture was stirred under an O_2 atmosphere at rt for 5 h. Sat. aq. NH_4Cl solution was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x), dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in MeCN/H_2O (1:3, 1.0 mL) and subjected to preparative HPLC separation using the conditions given below. Microsphaerospsisin B eluted at 39.6 min, microsphaeropsisin C at 52.4 min. Concentration of the fractions by rotary evaporator and lyophilizer gave microsphaeropsisin B (3.6 mg, 80 % pure, 10.9 µmol) as a slightly yellow solid and pure microsphaeropsisin C (6.6 mg, 25.0 µmol, 35%) as a colorless solid. Microsphaeropsisin B (3.6 mg, 80% pure, 10.9 µmol) was dissolved in MeCN/H_2O (2:3, 0.50 ml) and subjected to the

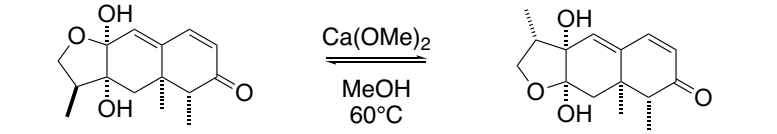
same preparative HPLC conditions. Microsphaerospsisin B eluted at 39.4 min and concentration of the collected fractions by rotary evaporator and lyophilizer gave pure microsphaeropsisin B (1.9 mg, 7.2 µmol, 10%) as a colorless solid.

Column: Synergi Hydro-RP 10 µm 80 Å, 250 x 21.2 mm; solvent A: H_2O; solvent B: MeCN; flow = 20.0 mL/min; T = rt; UV detection at 254 nm and 225 nm; solvent system: isocratic, [B] = 10 %.

Microsphaeropsisin C (3.3/3.3'): M.p. = 57.1 – 58.2°C. TLC: R_f = 0.45 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{24}$ = +67.0° (c = 0.48, MeOH). **FTIR** (neat): $\tilde{\nu}$ = 3412, 2968, 1669, 1455, 1393, 1224, 1096, 1077, 1014, 982, 863 cm^{-1}. **UV/Vis** (MeOH): λ_{max} 282 (3.94). **CD** (MeOH): 278 (28.6), 336 (–8.7). **^{1}H NMR** (500 MHz, MeOD-*d*$_4$, signals from the closed form are marked with [a], those from the open form with [b]; ratio a/b = 4:1): H NMR (500 MHz, Methanol-*d*$_4$) δ = 7.19[b] (d, *J* = 9.8, 1H), 7.05[a] (d, *J* = 9.8, 1H), 6.20[b] (d, *J* = 10.0, 1H), 6.18[b] (s, 1H), 5.97[a] (s, 1H), 5.96[a] (d, *J* = 9.4, 1H), 4.07[a] (t, *J* = 8.5, 1H), 3.47 – 3.38[b] (m, 2H), 3.34[a] (dd, *J* = 10.6, 8.5, 1H), 2.69[b] (q, *J* = 6.8, 1H), 2.61 – 2.53[a] (m, 1H), 2.44[a] (q, *J* = 6.8, 1H), 2.44 – 2.40[b] (m, 1H), 2.09[b] (d, *J* = 14.4, 1H), 1.97[b] (d, *J* = 14.3, 1H), 1.91[a] (d, *J* = 13.9, 1H), 1.51[a] (d, *J* = 14.0, 1H), 1.28[b] (s, 3H), 1.19[a] (s, 3H), 1.14[b] (d, *J* = 6.8, 3H), 1.10[a] (d, *J* = 6.8, 3H), 1.03[a+b] (d, *J* = 7.0, 6H). **^{1}H NMR** (500 MHz, DMSO-*d*$_6$, signals from the closed form are marked with [a], those from the open form with [b]; ratio a/b = 1.9:1)) δ = 7.27[b] (d, *J* = 10.0, 1H), 7.08[a] (d, *J* = 9.8, 1H), 6.37[a] (s, 1H), 6.20[b] (d, *J* = 9.7, 1H), 6.20[b] (s, 1H), 5.95[a] (s, 1H), 5.91[a] (d, *J* = 9.8, 1H), 5.11[b] (d, *J* = 1.7, 1H), 4.46[b] (t, *J* = 5.1, 1H), 4.10[a] (s, 1H), 3.91[a] (t, *J* = 8.4, 1H), 3.23 – 3.20[a+b] (m, 2H), 3.17 – 3.11[b] (m, 1H), 2.66[b] (q, *J* = 6.7, 1H), 2.48 – 2.41[a] (m, 1H), 2.35[a] (q, *J* = 6.9, 1H), 2.34 – 2.29[b] (m, 1H), 1.91[b] (d, *J* = 14.2, 1H), 1.81[b] (d, *J* = 14.3, 1H), 1.71[a] (d, *J* = 13.9, 1H), 1.40[a] (d, *J* = 13.8, 1H), 1.16[b] (s, 3H), 1.07[a] (s, 3H), 1.01[b] (d, *J* = 6.7, 3H), 0.98[a] (d, *J* = 6.8, 3H), 0.92[a] (d, *J* = 6.9, 3H), 0.91[b] (d, *J* = 6.9, 3H). **^{13}C NMR** (126 MHz, MeOD-*d*$_4$, signals from the closed form are marked with [a], those from the open form with [b]) δ = 203.4[a], 202.2[b], 200.9[b], 160.8[b], 146.1[a], 143.8[b], 142.4[a], 132.8[b], 132.2[a], 129.4[b], 128.4[a], 100.3[a], 77.6[a], 75.4[b], 71.6[a], 64.9[b], 54.4[a], 53.7[b], 43.9[a], 43.9[b], 41.5[b], 41.2[b], 40.4[a], 38.9[a], 22.7[b], 20.9[a], 11.0[b], 9.2[a], 7.5[b], 7.5[a]. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{20}O_4Na^+$ $[M+Na]^+$: 287.12538, found: 287.12540.

Microsphaeropsisin B (3.2/3.2'): M.p. = 165.7 – 168.1°C. TLC: R_f = 0.45 (SiO_2, Et_2O). Optical rotation: $[\alpha]_D^{25}$ = –20.2° (c = 0.60, MeOH). **FTIR** (neat): $\tilde{\nu}$ = 3402, 2965, 2934, 1667, 1584, 1458, 1394, 1254, 1212, 1080, 1009, 865 cm^{-1}. **^{1}H NMR** (500 MHz, MeOD-*d*$_4$, only signals from the closed form are shown since ratio closed/open = 7:1) δ = 7.05 (d, *J* = 9.8, 1H), 6.11 (s, 1H), 5.85 (d, *J* = 9.8, 1H), 4.08 (t, *J* = 8.5, 1H), 3.35 (dd, *J* = 10.5, 8.5, 4H), 2.60 –

2.55 (m, 1H), 2.25 (q, *J* = 7.2, 1H), 1.80 (d, *J* = 14.0, 1H), 1.44 (d, *J* = 14.1, 1H), 1.37 (s, 3H), 1.02 (d, *J* = 7.0, 3H), 0.97 (d, *J* = 7.1, 3H). **^{1}H NMR** (500 MHz, DMSO-d_6, signals from the closed form are marked with [a], those from the open form with [b]; ratio a/b = 2.4:1) δ = 7.28[b] (d, *J* = 9.8, 1H), 7.07[a] (d, *J* = 9.8, 1H), 6.39[a] (s, 1H), 6.30[b] (s, 1H), 6.09[b] (d, *J* = 10.0, 1H), 6.09[a] (s, 1H), 5.79[a] (d, *J* = 9.7, 1H), 5.15[b] (s, 1H), 4.49[b] (s, 1H), 4.14[a] (s, 1H), 3.92[a] (t, *J* = 8.4, 1H), 3.25 – 3.21[b] (m, 1H), 3.23[a] (dd, *J* = 10.4, 8.4, 1H), 3.18 – 3.15[b] (m, 1H), 2.56 – 2.43[a+b] (m, 2H), 2.38 – 2.32[b] (m, 1H), 2.15[a] (q, *J* = 7.2, 1H), 2.06[b] (d, *J* = 14.4, 1H), 1.63[a] (d, *J* = 13.9, 1H), 1.52[b] (d, *J* = 14.3, 1H), 1.35[b] (s, 3H), 1.28[a] (d, *J* = 13.9, 1H), 1.26[a] (s, 3H), 0.93[b] (d, *J* = 7.2, 3H), 0.92[b] (d, *J* = 7.1, 3H), 0.91[a] (d, *J* = 6.9, 3H), 0.84[a] (d, *J* = 7.1, 3H). **^{1}H NMR** (500 MHz, $CDCl_3$, only signals from the closed form are shown) δ = 6.89 (d, *J*=9.8, 1H), 6.00 (s, 1H), 5.90 (d, *J*=9.8, 1H), 4.15 (t, *J*=8.6, 1H), 3.40 (dd, *J*=10.8, 8.7, 1H), 2.75 (s, 1H), 2.56 – 2.49 (m, 1H), 2.47 (d, *J*=2.0, 1H), 2.32 (q, *J*=7.3, 1H), 1.76 (dd, *J*=14.2, 1.7, 1H), 1.49 (d, *J*=14.2, 1H), 1.41 (s, 3H), 1.05 (d, *J*=7.0, 3H), 0.99 (d, *J*=7.2, 3H). **^{13}C NMR** (126 MHz, MeOD-d_4, only signals from the closed form are shown) δ = 206.8, 146.6, 139.4, 135.3, 126.3, 100.5, 77.8, 71.8, 55.0, 43.8, 39.9, 34.6, 28.0, 14.8, 9.2. **^{13}C NMR** (126 MHz, $CDCl_3$, only signals from the closed form are shown) δ = 203.9, 143.6, 139.2, 131.7, 126.3, 99.3, 77.1, 71.3, 53.6, 43.3, 38.8, 33.0, 27.7, 14.4, 8.9. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{20}O_4Na^+$ $[M+Na]^+$: 287.12538, found: 287.12538.

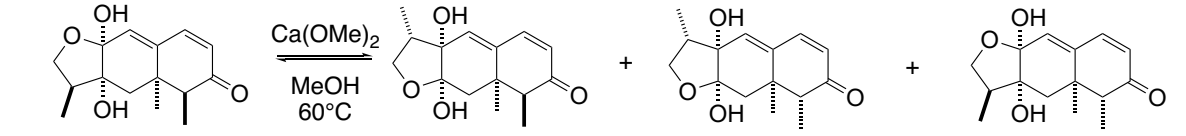


Microsphaeropsisin C **(3.3)** ***4-epi-Periconianone C*** **(3.11)**
38 % (75 % brsm)

4-*epi*-Periconianone C (**3.11/3.11'**): A solution of **3.3/3.3'** (8.2 mg, 31.0 µmol, 1.0 equiv.) and $Ca(OMe)_2$ (6.5 mg, 62.0 µmol, 2.0 equiv.) in MeOH (3.5 mL) was stirred at 60°C for 14 h. Sat. aq. NH_4Cl solution was added slowly and the mixture was diluted with H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 1:5) to give **3.11/3.11'** (3.1 mg, 11.7 µmol, 38 %) and recovered starting material **3.3/3.3'** (3.0 mg, 11.3 µmol, 37 %) both as colorless solids.

M.p. = 144.2 – 144.9°C. TLC: R_f = 0.58 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{25}$ = +79.4° (c = 0.52, MeOH). **FTIR** (neat): $\tilde{\nu}$ = 3402, 2969, 1674, 1455, 1389, 1217, 1110, 1025, 983, 935, 905, 862, 715 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6, only signals from the closed form are

shown since ratio closed/open = 10:1) δ = 7.07 (d, *J* = 9.8, 1H), 5.99 (s, 1H), 5.89 (d, *J* = 9.7, 1H), 5.54 (s, 1H), 5.18 (s, 1H), 3.70 (t, *J* = 7.4, 1H), 3.53 (dd, *J* = 11.2, 7.4, 1H), 2.44 (q, *J* = 6.7, 1H), 2.28 – 2.20 (m, 1H), 2.05 (d, *J* = 13.7, 1H), 1.78 (d, *J* = 13.7, 1H), 0.99 (s, 3H), 0.94 (d, *J* = 6.6, 3H), 0.92 (d, *J* = 6.8, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6, only signals from the closed form are shown since ratio closed/open = 10:1) δ = 200.2, 144.5, 139.8, 133.7, 126.3, 102.9, 75.7, 70.1, 51.7, 45.6, 44.3, 39.9 (according to HMBC), 19.2, 9.0, 7.0. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{20}O_4Na^+$ $[M+Na]^+$: 287.12538, found: 287.12529.



Microsphaeropsisin B* (3.2)** ***Periconianone C* (3.1)** 22 % (65 % brsm) after HPLC ***4-epi-Periconianone C (**3.11**), 7 % ***Microsphaeropsisin C*** (**3.3**), 8 %

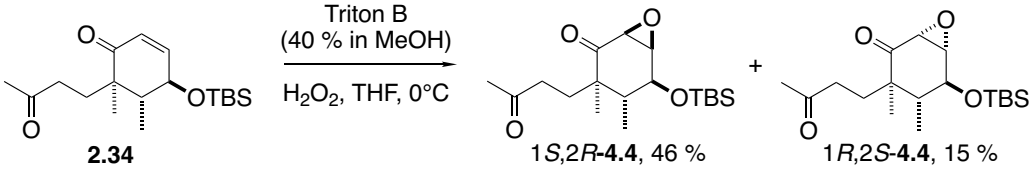
Periconianone C (3.1/3.1'): A solution of **3.2/3.2'** (1.4 mg, 5.3 µmol, 1.0 equiv.) and $Ca(OMe)_2$ (1.1 mg, 10.6 µmol, 2.0 equiv.) in MeOH (0.6 mL) was stirred at 60°C for 14 h. Sat. aq. NH_4Cl solution was added slowly and the mixture was diluted with H_2O and Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in MeOH/H_2O (2:1, 0.2 mL), separated in portions (5 x 40 µL) and subjected to semi-preparative HPLC separation using the conditions given below. Periconianone C eluted at 5.21 min, 4-*epi*-periconianone C at 6.57 min, microsphaeropsisin C at 4.39 min and microsphaeropsisin B at 3.59 min. Concentration of all fractions by rotary evaporator and lyophilizer gave periconianone C (0.31 mg, 1.2 µmol, 22 %), 4-*epi*-periconianone C (0.10 mg, 0.38 µmol, 7 %), microsphaeropsisin C (0.12 mg, 0.45 µmol, 8 %) and microsphaeropsisin B (0.61 mg, 2.3 µmol, 43 %) all as colorless solids.

Column: Synergi Hydro-RP 10 µm 80 Å, 150 x 10.0 mm; solvent A: H_2O; solvent B: MeCN; flow = 7.0 mL/min; T = rt; UV detection at 254 nm and 225 nm; solvent system: isocratic, [B] = 20 %.

TLC: R_f = 0.45 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{22}$ = –53.8° (c = 0.19, MeOH). **FTIR** (neat): $\tilde{\nu}$ = 3401, 2966, 2932, 2875, 1669, 1634, 1453, 1394, 1253, 1139, 1108, 1075, 1022, 986, 934, 905, 866, 719 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6, only signals from the closed form are shown since ratio closed/open = 5:1) δ = 7.06 (d, *J* = 9.7, 1H), 6.13 (s, 1H), 5.77 (d, *J* = 9.7, 1H), 5.61 (s, 1H), 5.23 (s, 1H), 3.73 (t, *J* = 7.4, 1H), 3.53 (dd, *J* = 11.1, 7.4, 1H), 2.22 – 2.12

(m, 1H), 2.07 (q, *J* = 7.2, 1H), 1.95 (d, *J* = 13.9, 1H), 1.65 (d, *J* = 13.8, 1H), 1.18 (s, 3H), 0.95 (d, *J* = 6.6, 3H), 0.87 (d, *J* = 7.1, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6, only signals from the closed form are shown since ratio closed/open = 5:1): δ = 203.0, 144.6, 136.8, 136.7, 124.2, 103.0, 76.1, 70.0, 52.5, 44.6, 41.7, 39.7 (according to HMBC), 26.1, 14.2, 9.1. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{20}O_4Na^+$ $[M+Na]^+$: 287.12538, found: 287.12527.

6.5 Guignarderemophilane C and D[229]



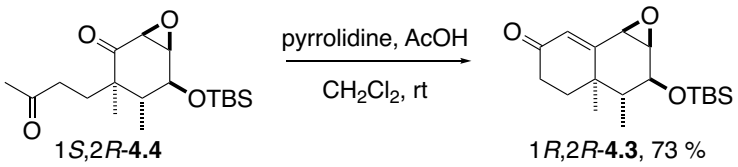
To a solution of enone **2.34** (53.5 mg, 0.16 mmol, 1.0 eq.) in H_2O_2 (30 % in H_2O, 1.55 mL, 16.5 mmol, 100 eq.) and THF (3.0 mL) at 0°C was added Triton B (40 % in MeOH, 90 µL, 0.19 mmol, 1.2 eq). The reaction mixture was stirred for 5 h 45 min at that temperature and then quenched by addition of sat. aq. NH_4Cl solution. The aqueous mixture was extracted with Et_2O (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (pentane/Et_2O 5:1) to give the α,β-epoxy ketones 1*S*,2*R*-**4.4** (26 mg, 76 µmol, 46 %) and 1*R*,2*S*-**4.4** (8.3 mg, 0.024 mmol, 15 %) both as colorless oils.

(1*S*,3*R*,4*R*,5*S*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3,4-dimethyl-3-(3-oxobutyl)-7-oxabicyclo[4.1.0]heptan-2-one (1*S*,2*R*-**4.4):**

TLC: R_f = 0.34 (SiO_2, pentane/Et_2O 5:1). **Optical rotation**: $[\alpha]_D^{26}$ = –112.9° (c = 0.40, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2956, 2931, 2857, 1714, 1472, 1362, 1256, 1083, 860, 838, 776 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 3.90 (dd, *J* = 10.1, 1.0 Hz, 1H), 3.50 (d, *J* = 4.0 Hz, 1H), 3.31 (d, *J* = 4.0 Hz, 1H), 2.34 (ddd, *J* = 16.8, 11.5, 4.8 Hz, 1H), 2.21 (ddd, *J* = 17.4, 11.4, 4.7 Hz, 1H), 2.14 – 2.08 (m, 1H), 2.11 (s, 3H), 2.00 (ddd, J = 14.3, 11.5, 4.7 Hz, 1H), 1.65 (ddd, J = 14.3, 11.4, 4.9 Hz, 1H), 0.94 (s, 9H), 0.92 (s, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.16 (s, 3H), 0.13 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 208.1, 208.1, 70.6, 57.7, 55.5, 49.0, 38.6, 32.9, 30.1, 29.9, 25.9 (3C), 20.2, 18.2, 10.9, -3.9, -4.5. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{33}O_4Si^+$ $[M+H]^+$: 341.21426, found: 341.21431.

(1*R*,3*R*,4*R*,5*S*,6*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3,4-dimethyl-3-(3-oxobutyl)-7-oxabicyclo[4.1.0]heptan-2-one (1*R*,2*S*-**4.4):**

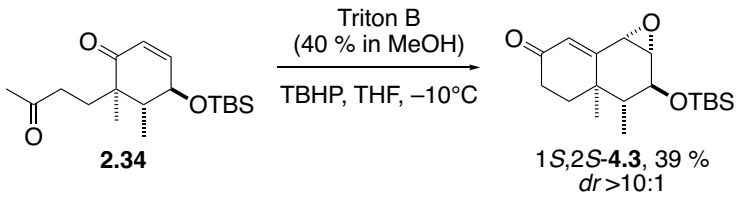
TLC: R_f = 0.40 (SiO_2, pentane/Et_2O 5:1). **Optical rotation**: $[\alpha]_D^{25}$ = +14.6° (c = 0.26, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2955, 2930, 2894, 2858, 1712, 1258, 1084, 876, 837, 777 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.01 (d, *J* = 7.2 Hz, 1H), 3.44 (dd, *J* = 3.5, 0.7 Hz, 1H), 3.25 (dd, *J* = 3.6, 0.9 Hz, 1H), 2.38 (ddd, *J* = 16.3, 11.1, 4.8 Hz, 1H), 2.25 (ddd, *J* = 16.8, 11.0, 4.9 Hz, 1H), 2.13 (s, 3H), 1.99 (ddd, *J* = 14.3, 11.0, 4.9 Hz, 2H), 1.85 (p, *J* = 7.1 Hz, 1H), 1.66 (ddd, *J* = 14.3, 11.1, 4.9 Hz, 1H), 1.08 (s, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.94 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 208.4 (2C), 70.4, 61.5, 54.1, 47.6, 44.0, 38.5, 30.5, 30.1, 25.9 (3C), 19.4, 18.2, 13.7, -4.3, -4.7. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{33}O_4Si^+$ $[M+H]^+$: 341.21426 found: 341.21428.



1*S*,2*R*-**4.4** 1*R*,2*R*-**4.3**, 73 %

(1a*R*,2*S*,3*R*,3a*R*,7b*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-3,3a-dimethyl-1a,3,3a,4,5,7b-hexahydronaphtho[1,2-*b*]oxiren-6(2*H*)-one (1*R*,2*R*-**4.3):** A mixture of α,β-epoxy ketone 1*S*,2*R*-**4.4** (8.5 mg, 25 µmol, 1.0 eq.), pyrrolidine (4 µL, 50 µmol, 2.0 eq.) and AcOH (3 µL, 50 µmol, 2.0 eq.) in CH_2Cl_2 (0.5 mL) was stirred for 2 h 20 min at rt, before it was quenched by addition of 0.1 M aq. HCl and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was subjected to flash column chromatography (pentane/Et_2O 3:1) to give the epoxy octalone 1*R*,2*R*-**4.3** (5.9 mg, 18 µmol, 73 %) as a colorless solid.

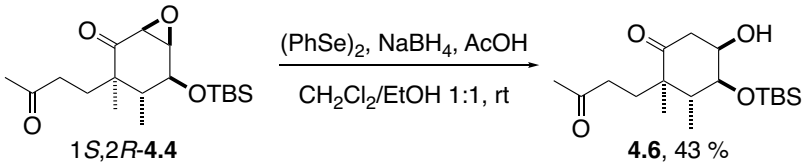
M.p. = 76.2 – 77.5°C. TLC: R_f = 0.34 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{25}$ = +30.7° (c = 0.36, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2954, 2928, 2856, 1682, 1472, 1258, 1084, 855, 836, 775 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.14 (s, 1H), 3.89 (dd, *J* = 10.0, 1.8 Hz, 1H), 3.56 (d, *J* = 3.7 Hz, 1H), 3.46 (dd, *J* = 3.7, 1.8 Hz, 1H), 2.52 (ddd, *J* = 18.1, 14.1, 5.5 Hz, 1H), 2.47 – 2.40 (m, 1H), 1.97 (ddd, *J* = 13.4, 5.4, 2.3 Hz, 1H), 1.75 (td, *J* = 13.8, 5.5 Hz, 1H), 1.66 (dq, *J* = 10.0, 6.9 Hz, 1H), 1.04 (s, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.94 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 198.4, 161.2, 131.1, 71.4, 56.1, 54.7, 38.2, 37.7, 34.1, 33.5, 26.0 (3C), 18.3, 17.1, 9.7, -3.8, -4.4. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{31}O_3Si^+$ $[M+H]^+$: 323.20370, found: 323.20360.



2.34 1*S*,2*S*-**4.3**, 39 %
dr >10:1

(1a*S*,2*S*,3*R*,3a*R*,7b*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3,3a-dimethyl-1a,3,3a,4,5,7b-hexahydronaphtho[1,2-*b*]oxiren-6(2*H*)-one (1*S*,2*S*-**4.3):** To a solution of TBS-protected enone **2.34** (21.0 mg, 65 µmol, 1.0 eq.) in THF (1.0 mL) at –10°C were added TBHP (5.5 M in decane, 59 µL, 0.32 mmol, 5.0 eq.) and Triton B (40 % in MeOH, 35 µL, 78 µmol, 1.2 eq.). The reaction mixture was stirred for 5 h 15 min at –10°C and then quenched by addition of sat. aq. NH_4Cl solution. The aqueous mixture was extracted with Et_2O (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was purified twice by flash column chromatography (pentane/Et_2O 5:1) to give epoxy octalone 1*S*,2*S*-**4.3** (8.2 mg, 25 µmol, 39 %) as a colorless solid.

M.p. = 107.4 – 110.1°C. TLC: R_f = 0.48 (SiO_2, pentane/Et_2O 5:1). **Optical rotation**: $[\alpha]_D^{26}$ = –39° (c = 0.36, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2954, 2930, 2885, 2858, 1686, 1472, 1258, 1086, 1065, 865, 837, 776 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.16 (s, 1H), 3.76 (d, *J* = 9.9 Hz, 1H), 3.48 (d, *J* = 3.6 Hz, 1H), 3.44 (d, *J* = 3.6 Hz, 1H), 2.57 (ddd, *J* = 17.6, 14.9, 5.0 Hz, 1H), 2.41 (d, *J* = 17.4 Hz, 1H), 1.99 – 1.95 (m, 1H), 1.68 (td, *J* = 14.1, 4.5 Hz, 1H), 1.44 (dd, *J* = 9.8, 6.7 Hz, 1H), 1.15 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.94 (s, 9H), 0.19 (s, 3H), 0.14 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 198.3, 161.8, 129.6, 70.1, 61.9, 56.5, 47.7, 36.7, 35.8, 33.9, 25.9 (3C), 18.1, 17.2, 11.7, -4.1, -4.7. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{31}O_3Si^+$ $[M+H]^+$: 323.20370, found: 323.20356.

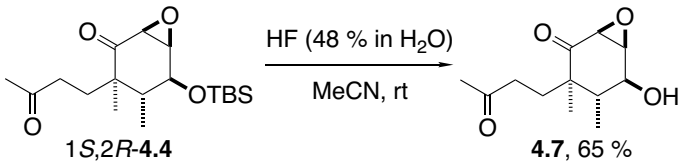


1*S*,2*R*-**4.4** **4.6**, 43 %

(2*R*,3*R*,4*S*,5*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-2,3-dimethyl-2-(3-oxobutyl)-cyclohexan-1-one (4.6): Stock solution: To a solution of diphenyl diselenide (89.5 mg, 287 mmol) in EtOH (1.0 mL) were added $NaBH_4$ (16.7 mg, 573 mmol) and AcOH (4.0 µL), and the mixture was stirred at rt for 20 min to form a yellow solution.

α,β-Epoxy ketone 1*S*,2*R*-**4.4** (13.0 mg, 38.0 µmol, 1.0 eq.) was dissolved in CH_2Cl_2 (0.2 mL) and the prepared stock solution (0.2 mL, 57 µmol, 1.5 eq) was added over a period of 5 min at rt. The reaction mixture turned yellow and was stirred for 1 h 10 min, before it was diluted with CH_2Cl_2 and brine. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (pentane/Et_2O 1:1) to give the β-hydroxy ketone **4.6** (5.6 mg, 16 µmol, 43 %) as a colorless oil.

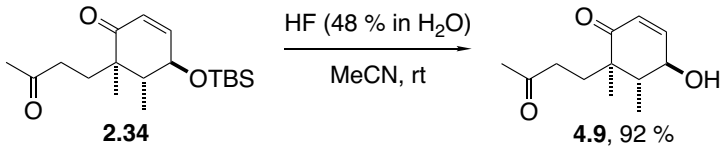
TLC: R_f = 0.50 (SiO_2, pentane/Et_2O 1:3). **Optical rotation**: $[\alpha]_D^{26}$ = +21.8° (c = 0.28, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3493, 2955, 2929, 2857, 1711, 1463, 1254, 1067, 837, 776 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 4.08 (q, *J* = 3.4 Hz, 1H), 3.82 (dd, *J* = 10.0, 2.7 Hz, 1H), 2.69 (ddd, *J* = 15.3, 3.4, 2.2 Hz, 1H), 2.57 (dd, *J* = 15.4, 3.6 Hz, 1H), 2.50 (ddd, *J* = 17.3, 11.2, 4.5 Hz, 1H), 2.40 (dd, *J* = 2.2, 1.0 Hz, 1H), 2.28 (ddd, *J* = 16.9, 11.1, 4.9 Hz, 1H), 2.17 – 2.08 (m, 1H), 2.14 (s, 3H), 1.97 (ddd, *J* = 14.3, 11.2, 4.5 Hz, 1H), 1.04 (s, 3H), 1.61 (ddd, *J* = 14.2, 11.1, 4.9 Hz, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 212.0, 209.0, 74.2, 71.5, 50.2, 42.5, 38.8, 36.4, 30.2, 28.7, 26.0 (3C), 20.6, 18.2, 11.7, -4.1, -4.4. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{35}O_4Si^+$ $[M+H]^+$: 343.22991, found: 343.22956.



(1*S*,3*R*,4*R*,5*S*,6*S*)-5-Hydroxy-3,4-dimethyl-3-(3-oxobutyl)-7-oxabi-cyclo[4.1.0]heptan-2-one (4.7): To a solution of α,β-epoxy ketone 1*S*,2*R*-**4.4** (9.0 mg, 26 µmol, 1.0 eq.) in MeCN (0.5 mL) was added HF (48 % in H_2O, 5 µL, 0.26 mmol, 10 eq.). The mixture was stirred for 3 h 15 min at rt before it was quenched by addition of sat. aq. $NaHCO_3$. The mixture was extracted with Et_2O (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 1:3 to 1:5 to 1:7) to afford the epoxy alcohol **4.7** (3.9 mg, 17 µmol, 65 %) as a colorless oil.

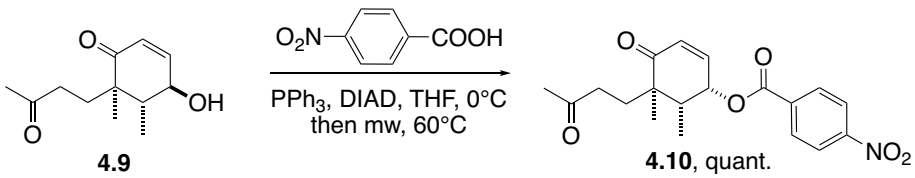
TLC: R_f = 0.50 (SiO_2, Et_2O). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.89 (ddd, *J* = 10.0, 8.6, 1.2 Hz, 1H), 3.67 (dd, *J* = 4.0, 1.1 Hz, 1H), 3.39 (d, *J* = 4.0 Hz, 1H), 2.40 – 2.18 (m, 2H), 2.12 (s, 3H), 2.09 – 1.94 (m, 2H), 1.78 (d, *J* = 8.6 Hz, 1H), 1.66 (ddd, *J* = 14.3, 10.5, 5.6 Hz, 1H), 1.02 (d, *J*

= 6.8 Hz, 3H), 0.94 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 207.9, 207.2, 70.2, 57.3, 55.6, 49.1, 38.6, 33.3, 30.1, 29.4, 20.0, 10.4. **HRMS** (ESI) Exact mass calculated for $C_{12}H_{18}O_4Na^+$ $[M+Na]^+$: 249.10973, found: 249.10979.



(4*R*,5*R*,6*R*)-4-Hydroxy-5,6-dimethyl-6-(3-oxobutyl)cyclohex-2-en-1-one (4.9): To a solution of TBS protected alcohol **2.34** (792 mg, 2.44 mmol, 1.0 eq.) in MeCN (36 mL) was added HF (48 % in H_2O, 1.0 mL, 24.4 mmol, 10 eq.). The mixture was stirred for 38 h at rt, before it was quenched by addition of sat. aq. $NaHCO_3$. The solution was extracted with Et_2O (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The crude material was subjected to flash column chromatography (Et_2O) to yield the allylic alcohol **4.9** (471 mg, 2.24 mmol, 92 %) as a colorless solid.

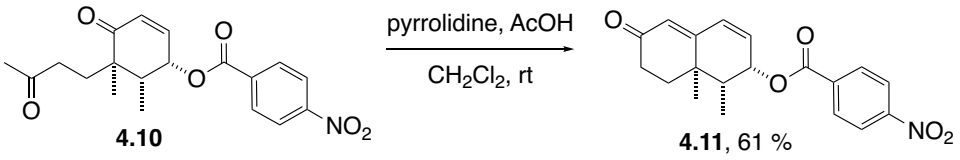
M.p. = 78.8 – 83.5°C. TLC: R_f = 0.38 (SiO_2, Et_2O). **Optical rotation**: $[\alpha]_D^{26}$ = –63.6° (c = 0.48, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3472, 2971, 2020, 1713, 1672, 1377, 1041 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.82 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.92 (dd, *J* = 10.2, 2.2 Hz, 1H), 4.22 (ddt, *J* = 9.4, 7.2, 2.1 Hz, 1H), 2.33 (ddd, *J* = 15.1, 11.3, 4.2 Hz, 1H), 2.27 – 2.19 (m, 1H), 2.19 – 2.09 (m, 1H), 2.14 (s, 3H), 1.96 (dq, *J* = 9.5, 6.7 Hz, 1H), 1.84 (d, *J* = 7.2 Hz, 1H), 1.62 (ddd, *J* = 14.0, 11.3, 4.1 Hz, 1H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.02 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 208.8, 203.2, 150.7, 127.9, 70.6, 48.5, 42.8, 38.5, 30.0, 28.4, 19.3, 10.8. **HRMS** (ESI) Exact mass calculated for $C_{12}H_{19}O_3^+$ $[M+H]^+$: 211.13287, found: 211.13286.



(1*S*,5*R*,6*R*)-5,6-Dimethyl-4-oxo-5-(3-oxobutyl)cyclohex-2-en-1-yl 4-nitrobenzoate (4.10): Triphenylphosphine (517 mg, 1.95 mmol, 2.0 eq.) and DIAD (0.383 mL, 1.95 mmol, 2.0 eq.) were dissolved in THF (4.5 mL) at 0°C. After 5 min allylic alcohol **4.9** (205 mg, 0.98 mmol, 1.0 eq.) in THF (7.5 mL) and 4-nitrobenzoic acid (329 mg, 1.95 mmol, 2.0 eq.) were added to

the reaction mixture. After stirring was continued for 5 min at 0°C, the reaction mixture was allowed to warm up to rt and was stirred for 35 min, before it was heated to 60°C for 1 h in the microwave. After evaporation of the solvent, the crude material was subjected to flash column chromatography (pentane/Et_2O 1:1) to give the ester **4.10** (345 mg, 0.98 mmol, quant.) as a colorless solid.

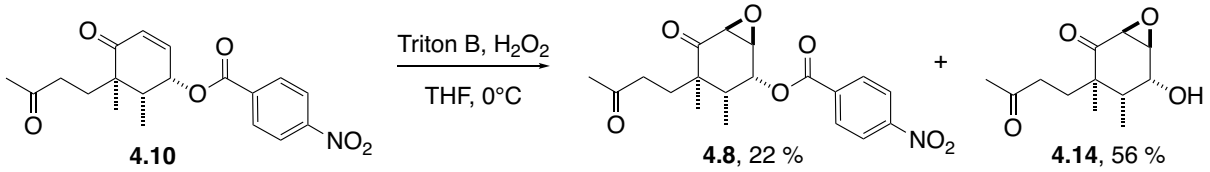
M.p. = 72.6 – 74.6°C. TLC: $\boldsymbol{R_f}$ = 0.25 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{26}$ = +159.2° (c = 0.47, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2982, 1723, 1682, 1528, 1348, 1270, 1102, 1066 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.34 – 8.29 (m, 2H), 8.24 – 8.20 (m, 2H), 6.74 (ddd, *J* = 10.2, 2.9, 1.5 Hz, 1H), 6.09 (dt, *J* = 5.1, 2.6 Hz, 1H), 6.06 (dd, *J* = 10.2, 2.1 Hz, 1H), 2.59 – 2.52 (m, 2H), 2.37 (ddd, *J* = 17.5, 10.5, 5.2 Hz, 1H), 2.17 (s, 3H), 2.02 (ddd, *J* = 14.4, 10.5, 5.3 Hz, 1H), 1.93 (ddd, *J* = 14.4, 10.6, 5.2 Hz, 1H), 1.16 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 207.7, 202.3, 164.0, 150.9, 142.6, 135.0, 130.9 (2C), 130.0, 123.9 (2C), 71.7, 49.2, 40.8, 38.4, 30.2, 29.6, 19.9, 10.1. **HRMS** (ESI) Exact mass calculated for $C_{19}H_{21}NO_6Na^+$ $[M+Na]^+$: 382.12611, found: 382.12626.



(1*R*,2*S*,8a*R*)-1,8a-Dimethyl-6-oxo-1,2,6,7,8,8a-hexahydro-naphthalen-2-yl 4-nitrobenzoate (4.11): A mixture of ester **4.10** (14.1 mg, 39 µmol, 1.0 eq.), pyrrolidine (6 µL, 78 µmol, 2.0 eq.) and AcOH (4.5 µL, 78 µmol, 2.0 eq.) in CH_2Cl_2 (0.4 mL) was stirred for 3 h 10 min at rt, before additional pyrrolidine (2.0 eq.) and AcOH (2.0 eq.) were added. After in total 9 h at rt the mixture was quenched by addition of 0.1 M aq. HCl and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Since the residue still contained enone **4.10** (monitored by ^{1}H NMR), a mixture of crude material, pyrrolidine (2.0 eq.) and AcOH (2.0 eq.) in CH_2Cl_2 (0.5 mL) was stirred for additional 14 h at rt. The same work-up procedure was carried out as described before and the obtained residue was subjected to flash column chromatography (pentane/Et_2O 1:1) to give the dienone **4.11** (8.1 mg, 24 µmol, 61 %) as a colorless solid.

M.p. = 162.3 – 163.6°C. TLC: $\boldsymbol{R_f}$ = 0.54 (SiO_2, pentane/Et_2O 1:2). **Optical rotation**: $[\alpha]_D^{26}$ = +699° (c = 0.41, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3111, 2971, 2944, 1721, 1663, 1527, 1268, 1093,

719 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 8.7 Hz, 2H), 8.18 (d, *J* = 8.6 Hz, 2H), 6.41 (d, *J* = 9.7 Hz, 1H), 6.33 (dd, *J* = 9.7, 5.2 Hz, 1H), 5.85 (s, 1H), 5.64 (t, *J* = 4.9 Hz, 1H), 2.61 (ddd, *J* = 18.0, 14.2, 5.4 Hz, 1H), 2.52 (ddd, *J* = 18.0, 5.3, 2.1 Hz, 1H), 2.14 (ddd, *J* = 13.4, 5.4, 2.2 Hz, 1H), 2.08 (dd, *J* = 7.2, 4.7 Hz, 1H), 1.81 (td, *J* = 13.8, 5.2 Hz, 1H), 1.41 (s, 3H), 1.12 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 199.2, 164.5, 160.7, 150.8, 135.5, 132.4, 131.4, 130.8 (2C), 126.6, 123.9 (2C), 71.5, 41.1, 35.8, 34.3, 34.1, 18.4, 10.5. **HRMS** (ESI) Exact mass calculated for $C_{19}H_{20}NO_5^+$ $[M+H]^+$: 342.13360, found: 342.13368.



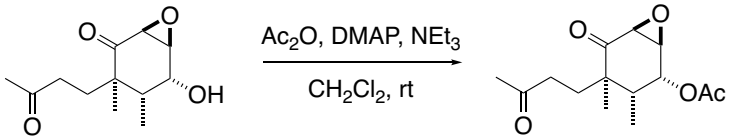
Ester **4.10** (25.6 mg, 71 µmol, 1.0 eq.) was dissolved in THF (1.5 mL) and cooled to 0°C. H_2O_2 (30 % in H_2O, 675 µL, 7.12 mmol, 100 eq.) and Triton B (40 % in MeOH, 32 µL, 71 µmol, 1.0 eq.) were added and the reaction mixture was stirred for 2 h 40 min at 0°C, before it was quenched by addition of sat. aq. Na_2CO_3 and diluted with Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude residue was subjected to flash column chromatography (Et_2O/pentane 2:1) to give the epoxy ester **4.8** (5.80 mg, 15 µmol, 22 %) as a colorless solid and epoxy alcohol **4.14** (9.0 mg, 40 µmol, 56 %) as a colorless oil.

(1*S*,2*R*,3*R*,4*R*,6*S*)-3,4-Dimethyl-5-oxo-4-(3-oxobutyl)-7-oxabi-cyclo[4.1.0]heptan-2-yl 4-nitrobenzoate (4.8):

M.p. = 112.2 – 113.9°C. TLC: R_f = 0.43 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = +27.9° (c = 0.29, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2919, 1714, 1528, 1348, 1266, 1099, 718 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 8.8 Hz, 2H), 8.15 – 8.12 (m, 2H), 5.74 (t, *J* = 3.0 Hz, 1H), 3.85 (t, *J* = 3.6 Hz, 1H), 3.45 (d, *J* = 4.0 Hz, 1H), 2.56 (qd, *J* = 7.3, 2.9 Hz, 1H), 2.48 – 2.32 (m, 2H), 2.15 (s, 3H), 1.95 (ddd, *J* = 15.4, 9.9, 5.6 Hz, 1H), 1.86 (ddd, *J* = 14.7, 9.9, 5.8 Hz, 1H), 1.19 (s, 3H), 1.04 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 208.8, 207.7, 164.5, 151.0, 134.6, 131.0 (2C), 124.0 (2C), 74.2, 55.1, 54.4, 48.1, 38.4, 33.5, 31.8, 30.3, 21.2, 11.8. **HRMS** (ESI) Exact mass calculated for $C_{19}H_{21}O_7NNa^+$ $[M+Na]^+$: 398.12102, found: 398.12103.

(1*S*,3*R*,4*R*,5*R*,6*S*)-5-Hydroxy-3,4-dimethyl-3-(3-oxobutyl)-7-oxabi-cyclo[4.1.0]heptan-2-one (4.14):

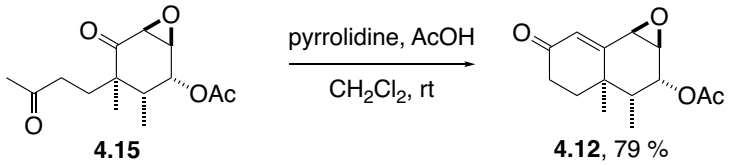
TLC: R_f = 0.27 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{25}$ = –65.5° (c = 0.20, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3481, 2917, 2849, 1700, 1369, 1259, 1167 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 4.34 (d, *J* = 3.9 Hz, 1H), 3.64 (t, *J* = 3.6 Hz, 1H), 3.36 (d, *J* = 3.9 Hz, 1H), 2.38 (ddd, *J* = 16.4, 10.5, 5.4 Hz, 1H), 2.33 – 2.25 (m, 1H), 2.17 (qd, *J* = 7.4, 2.7 Hz, 1H), 2.12 (s, 3H), 2.04 (d, *J* = 4.6 Hz, 1H), 1.85 (ddd, *J* = 13.9, 10.5, 5.3 Hz, 1H), 1.74 (ddd, *J* = 14.0, 10.4, 5.4 Hz, 1H), 1.09 (s, 3H), 1.03 (dd, *J* = 7.3, 1.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 209.9, 208.4, 70.6, 57.0, 54.9, 48.0, 38.7, 33.8, 31.7, 30.2, 21.8, 11.5. **HRMS** (ESI) Exact mass calculated for $C_{12}H_{19}O_4^+$ $[M+H]^+$: 227.12779, found: 227.12784.



4.14 **4.15**, 88 %

(1*S*,2*R*,3*R*,4*R*,6*S*)-3,4-Dimethyl-5-oxo-4-(3-oxobutyl)-7-oxabi-cyclo[4.1.0]heptan-2-yl acetate (4.15): To a solution of epoxy alcohol **4.14** (102 mg, 0.45 mmol, 1.0 eq.) in CH_2Cl_2 (4.0 mL) was added Et_3N (127 µL, 0.90 mmol, 2.0 eq.), Ac_2O (0.17 mL, 1.8 mmol, 4.0 eq.) and DMAP (5.5 mg, 45 µmol, 0.1 eq.). The resulting mixture was stirred at rt for 1 h, then quenched by addition of 0.1 M HCl and diluted with CH_2Cl_2. After the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was subjected to flash column chromatography (pentane/Et_2O 1:1) to afford acetate **4.15** (107 mg, 0.40 mmol, 88 %) as a colorless solid.

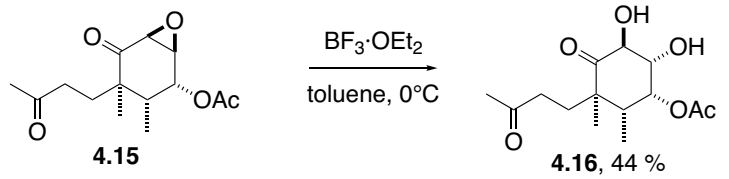
M.p. = 71.8 – 73.9°C. TLC: R_f = 0.45 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{25}$ = –14.5° (c = 0.23, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2918, 2849, 1745, 1700, 1462, 1369, 1227, 1016, 977 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.43 (t, *J* = 3.1 Hz, 1H), 3.72 – 3.68 (m, 1H), 3.36 (d, *J* = 3.9 Hz, 1H), 2.46 – 2.26 (m, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.88 (ddd, *J* = 14.3, 10.1, 5.5 Hz, 1H), 1.77 (ddd, *J* = 14.3, 10.2, 5.7 Hz, 1H), 1.08 (s, 3H), 0.95 (d, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = (126 MHz, $CDCl_3$) δ = 209.3, 207.9, 170.6, 72.3, 55.0, 54.5, 48.1, 38.5, 32.7, 31.8, 30.2, 21.2, 20.9, 11.5. **HRMS** (ESI) Exact mass calculated for $C_{14}H_{20}O_5Na^+$ $[M+Na]^+$: 291.12029, found: 291.12025.



4.15 **4.12**, 79 %

(1a*S*,2*R*,3*R*,3a*R*,7b*R*)-3,3a-Dimethyl-6-oxo-1a,2,3,3a,4,5,6,7b-octahydronaphtho[1,2-*b*]-oxiren-2-yl acetate (4.12): A mixture of α,β-epoxy ketone **4.15** (19.3 mg, 72 µmol, 1.0 eq), pyrrolidine (12 µL, 0.14 mmol, 2.0 eq.) and AcOH (8.2 µL, 0.14 mmol, 2.0 eq) in CH_2Cl_2 (0.6 mL) was stirred at rt o.n. The mixture was quenched by addition of 0.1 M aq. HCl and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was subjected to flash column chromatography (pentane/Et_2O 1:1) to yield epoxy octalone **4.12** (14.2 mg, 57 µmol, 79 %) as a colorless solid.

M.p. = 81.8 – 85.8°C. TLC: R_f = 0.44 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[a]_D^{23}$ = +212.6° (c = 0.62, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2923, 2853, 1744, 1681, 1374, 1230, 1026 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.17 (s, 1H), 5.42 – 5.39 (m, 1H), 3.56 (d, *J* = 3.3 Hz, 1H), 3.50 (dd, *J* = 3.3, 2.1 Hz, 1H), 2.60 (ddd, *J* = 18.3, 14.1, 5.6 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.15 (s, 3H), 1.99 (ddd, *J* = 13.3, 5.4, 2.2 Hz, 1H), 1.87 (qd, *J* = 7.3, 3.9 Hz, 1H), 1.71 (td, *J* = 13.7, 5.4 Hz, 1H), 1.21 (s, 3H), 0.94 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 198.1, 170.4, 160.6, 131.7, 70.8, 53.0, 53.0, 35.6, 34.7, 34.1, 34.0, 21.1, 18.8, 9.8. **HRMS** (ESI) Exact mass calculated for $C_{14}H_{19}O_4^+$ $[M+H]^+$: 251.12779, found: 251.12786.

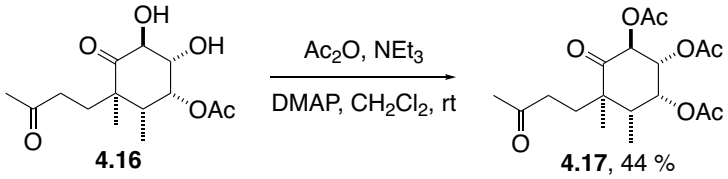


4.15 **4.16**, 44 %

(1*R*,2*R*,3*R*,5*S*,6*S*)-5,6-Dihydroxy-2,3-dimethyl-4-oxo-3-(3-oxo-butyl)cyclohexyl acetate (4.16): A solution of epoxy ketone **4.15** (108 mg, 0.40 mmol, 1.0 eq.) in toluene (4.5 mL) was cooled to 0°C and $BF_3 \cdot Et_2O$ (56.2 µL, 0.44 mmol, 1.1 eq.) was added. The resulting yellow solution was stirred for 7 h and then quenched by addition of sat. aq. $NaHCO_3$. The mixture was extracted with EtOAc (3 x) and the combined organic layers were dried over Na_2SO_4,

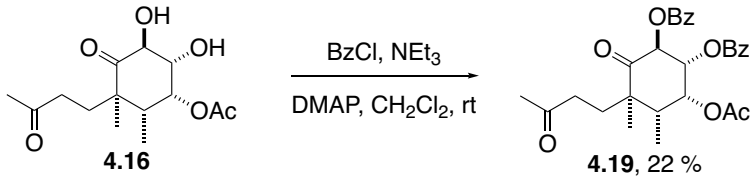
filtered and concentrated. The crude material was subjected to flash column chromatography (EtOAc) to give the 1,2-diol **4.16** (50.4 mg, 0.18 mmol, 44 %) as a colorless oil.

TLC: R_f = 0.25 (SiO_2, EtOAc). **Optical rotation**: $[\alpha]_D^{24} = -1.5°$ (c = 0.21, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3453, 2918, 2848, 1743, 1713, 1375, 1238, 1103, 1005 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.50 (t, *J* = 3.3 Hz, 1H), 4.60 (d, *J* = 10.8 Hz, 1H), 3.59 (dd, *J* = 10.8, 3.4 Hz, 1H), 3.52 (brs, 1H), 2.58 (brs, 1H), 2.47 – 2.28 (m, 2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.01 (ddd, *J* = 15.2, 10.3, 5.3 Hz, 1H), 1.88 (qd, *J* = 7.0, 3.1 Hz, 1H), 1.65 (ddd, *J* = 14.5, 10.4, 5.3 Hz, 1H), 1.26 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 211.9, 208.1, 170.8, 75.5, 73.9, 73.9, 49.5, 38.9, 36.2, 30.2, 29.2, 21.3, 21.1, 10.9. **HRMS** (ESI) Exact mass calculated for $C_{14}H_{22}O_6Na^+$ $[M+Na]^+$: 309.13086, found: 309.13086.



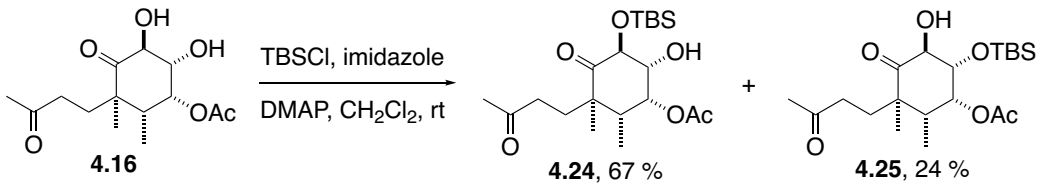
(1*S*,2*R*,3*R*,4*R*,5*R*)-4,5-Dimethyl-6-oxo-5-(3-oxobutyl)cyclohexane-1,2,3-triyl triacetate (4.17): To a solution of 1,2-diol **4.16** (3.9 mg, 14 µmol, 1.0 eq.) in CH_2Cl_2 (0.3 mL) was added Et_3N (6 µL, 41 µmol, 3.0 eq.), Ac_2O (9 µL, 95 µmol, 7.0 eq.) and DMAP (0.3 mg, 2.7 µmol, 0.2 eq.) at rt. The resulting mixture was stirred at rt for 1 h, then quenched by addition of a 0.1 M aq. HCl solution and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was subjected to flash column chromatography (pentane/Et_2O 1:2) to afford the tri-acetylated compound **4.17** (2.2 mg, 6.0 µmol, 44 %) as a colorless oil.

TLC: R_f = 0.39 (SiO_2, pentane/Et_2O 1:2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.72 (d, *J* = 12.0 Hz, 1H), 5.55 (t, *J* = 3.2 Hz, 1H), 5.08 (dd, *J* = 12.0, 3.4 Hz, 1H), 2.42 (ddd, *J* = 16.3, 10.7, 5.1 Hz, 1H), 2.36 – 2.26 (m, 1H), 2.19 (s, 3H), 2.17 (s, 3H), 2.15 (s, 3H), 2.02 (s, 3H), 2.00 – 1.91 (m, 2H), 1.62 (ddd, *J* = 14.5, 10.6, 5.2 Hz, 1H), 1.30 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 208.0, 204.3, 170.3, 170.2, 169.8, 72.9, 72.5, 71.2, 50.6, 38.8, 35.3, 30.1, 29.3, 21.0, 21.0, 20.8, 20.7, 10.8. **HRMS** (ESI) Exact mass calculated for $C_{18}H_{26}O_8Na^+$ $[M+Na]^+$: 393.15199, found: 393.15203.



(1*R*,2*S*,4*R*,5*R*,6*R*)-6-Acetoxy-4,5-dimethyl-3-oxo-4-(3-oxobutyl)-cyclohexane-1,2-diyl dibenzoate (4.19): To a solution of 1,2-diol **4.16** (3.7 mg, 13 µmol, 1.0 eq.) in CH_2Cl_2 (0.3 mL) was added Et_3N (3.7 µL, 26 µmol, 2.0 eq.), BzCl (6.0 µL, 52 µmol, 4.0 eq.) and DMAP (0.15 mg, 1.3 µmol, 0.1 eq.) at 0°C. The reaction mixture was allowed to warm up to rt and stirred for 2 h 15 min, before additional BzCl (20 µL, 0.17 mmol, 13 eq.) was added. After stirring for 19 h at rt, additional Et_3N (7 µL, 52 µmol, 4.0 eq.) was added to the mixture and the solvent was evaporated after the mixture was stirred for in total 23 h 15 min. The residue was subjected to flash column chromatography (SiO_2, pentane/Et_2O 1:1) to afford the dibenzylated product **4.19** (1.4 mg, 3 µmol, 22 %) as a colorless solid.

M.p. = 131.3 – 134.4°C. TLC: $\boldsymbol{R_f}$ = 0.34 (SiO_2, pentane/Et_2O, 1:1). **Optical rotation**: $[\alpha]_D^{24}$ = –39.0° (c = 1.10, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2926, 1720, 1452, 1267, 1224, 1094, 710 cm^{-1}. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ = 8.04 – 7.99 (m, 2H), 7.93 – 7.88 (m, 2H), 7.56 – 7.51 (m, 2H), 7.43 – 7.36 (m, 4H), 6.17 (d, *J* = 11.9, 1H), 5.78 (t, *J* = 3.3, 1H), 5.56 (dd, *J* = 11.9, 3.5, 1H), 2.49 (ddd, *J* = 16.1, 10.8, 4.9, 1H), 2.38 (ddd, *J* = 16.8, 10.6, 5.0, 1H), 2.22 (s, 3H), 2.15 (s, 3H), 2.10 (qd, *J* = 7.2, 3.3, 1H), 2.04 (td, *J* = 10.3, 5.3, 1H), 1.68 (ddd, *J* = 14.4, 10.7, 5.0, 1H), 1.42 (s, 3H), 1.10 (d, *J* = 6.9, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 208.2, 204.1, 170.0, 165.9, 165.4, 133.6 (2C), 130.0 (2C), 129.8 (2C), 129.2, 129.1, 128.6 (2C), 128.6 (2C), 73.7, 72.6, 71.8, 50.7, 38.9, 35.7, 30.2, 29.4, 21.0 (2C), 10.9. **HRMS** (ESI) Exact mass calculated for $C_{28}H_{30}O_8Na^+$ $[M+H]^+$: 517.18328, found: 517.18333.



To a solution of 1,2-diol **4.16** (22.3 mg, 78 µmol, 1.0 eq), imidazole (13.3 mg, 0.20 mmol, 2.5 eq) and DMAP (4.8 mg, 39 µmol 0.5 eq.) in CH_2Cl_2 (0.9 mL) was added TBSCl (47.5 mg, 0.31 µmol, 4.0 eq) and the mixture was stirred at rt for 15 h. The reaction mixture was quenched by addition of sat. aq. NH_4Cl solution, and extracted with CH_2Cl_2 (3 x). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The crude

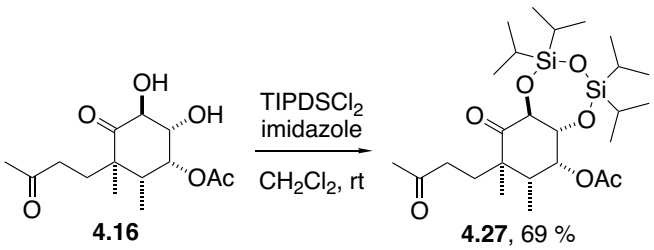
material was subjected to flash column chromatography (pentane/Et_2O, 1:2) to afford the silyl ether **4.24** (20.8 mg, 51.9 µmol, 67 %) as a colorless oil and impure **4.25**. After a second flash column chromatography (pentane/Et_2O 4:1 to 2:1 to 1:1) silyl ether **4.25** (7.5 mg, 18.7 µmol, 24 %) was obtained as a colorless solid.

(1*R*,2*R*,3*R*,5*S*,6*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-hydroxy-2,3-dimethyl-4-oxo-3-(3-oxobutyl)cyclohexyl acetate (4.24):

TLC: R_f = 0.21 (SiO_2, pentane/Et_2O 1:2). **Optical rotation**: $[\alpha]_D^{23}$ = –31.7° (c = 0.99, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3483, 2930, 2857, 1747, 1711, 1234, 1126, 1007, 839, 781 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.55 (t, *J* = 3.3, 1H), 4.66 (d, *J* = 10.7, 1H), 3.67 (ddd, *J* = 10.7, 3.3, 1.3, 1H), 2.46 (ddd, *J* = 17.0, 11.0, 4.7, 1H), 2.39 (s, 1H), 2.26 (ddd, *J* = 16.9, 11.0, 5.0, 1H), 2.17 (s, 3H), 2.14 (s, 3H), 1.95 (ddd, *J* = 14.4, 11.0, 4.7, 1H), 1.85 (qd, *J* = 7.0, 3.2, 1H), 1.57 (ddd, *J* = 14.4, 11.0, 5.0, 1H), 1.21 (s, 3H), 1.00 (d, *J* = 7.1, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 210.0, 208.4, 170.6, 75.9, 74.2, 73.9, 50.5, 38.9, 35.5, 30.1, 29.3, 26.0 (3C), 21.8, 21.1, 18.8, 10.8, -4.3, -5.5. HRMS (ESI) Exact mass calculated for $C_{20}H_{37}O_6Si^+$ $[M+H]^+$: 401.23539, found: 401.23538 and for $C_{20}H_{36}O_6SiNa^+$ $[M+Na]^+$: 423.21734, found: 423.21699.

(1*R*,2*R*,3*R*,5*S*,6*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-2,3-dimethyl-4-oxo-3-(3-oxobutyl)cyclohexyl acetate (4.25):

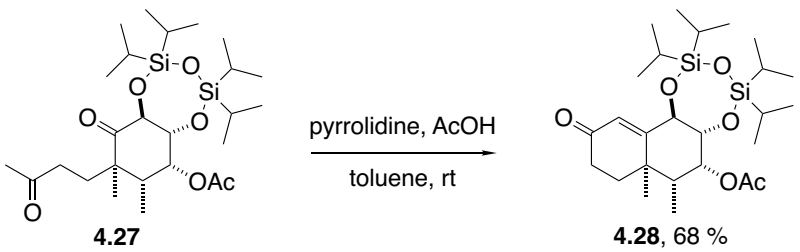
M.p. = 97.1 – 99.3°C. TLC: R_f = 0.65 (SiO_2, pentane/Et_2O 1:2). **Optical rotation**: $[\alpha]_D^{24}$ = –7.1° (c = 0.31, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3492, 2930, 2857, 1746, 1720, 1372, 1237, 1165, 1010, 838, 781 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.37 (t, *J* = 3.3, 1H), 4.56 (dd, *J* = 10.4, 3.9, 1H), 3.50 (dd, *J* = 10.4, 3.6, 1H), 3.43 (d, *J* = 4.0, 1H), 2.42 (ddd, *J* = 16.1, 10.7, 5.1, 1H), 2.34 (ddd, *J* = 16.9, 10.6, 5.2, 1H), 2.16 (s, 3H), 2.14 (s, 3H), 1.99 (ddd, *J* = 14.4, 10.5, 5.0, 1H), 1.81 (qd, *J* = 7.0, 3.1, 1H), 1.63 (ddd, *J* = 14.4, 10.7, 5.2, 1H), 1.23 (s, 3H), 1.01 (d, *J* = 7.0, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 212.8, 208.2, 170.3, 76.3, 75.2, 74.5, 49.3, 38.9, 35.8, 30.2, 29.3, 25.7 (3C), 21.1 (2C), 18.3, 10.8, -4.5, -5.0. **HRMS** (ESI) Exact mass calculated for $C_{20}H_{36}O_6SiNa^+$ $[M+Na]^+$: 423.21734, found: 423.21744.



4.16 **4.27**, 69 %

(5a*R*,6*R*,7*R*,8*R*,9a*S*)-2,2,4,4-Tetraisopropyl-7,8-dimethyl-9-oxo-8-(3-oxobutyl)-hexahydrobenzo[*f*][1,3,5,2,4]trioxadisilepin-6-yl acetate (4.27): 1,2-Diol **4.16** (50.4 mg, 0.18 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1.0 mL), before imidazole (48.0 mg, 0.70 mmol, 4.0 eq.) and $TIPDSCl_2$ (67 µL, 0.21 mmol, 1.2 eq.) were added. The turbid mixture was stirred for 9 h 15 min, before it was diluted by addition of sat. aq. NH_4Cl solution and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to afford fully protected triol **4.27** (64.1 mg, 0.12 mmol, 69 %) as a colorless oil.

TLC: R_f = 0.67 (SiO_2, pentane/Et_2O 1:1). **Optical rotation**: $[\alpha]_D^{22}$ = +10.2° (c = 0.57, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 3514, 2945, 2867, 1755, 1727, 1464, 1367, 1234, 1165, 1054, 985 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.50 (t, *J* = 3.5 Hz, 1H), 4.79 (d, *J* = 10.1 Hz, 1H), 3.82 (dd, *J* = 10.2, 3.7 Hz, 1H), 2.47 (ddd, *J* = 16.1, 11.1, 4.6 Hz, 1H), 2.31 (ddd, *J* = 16.6, 11.1, 4.9 Hz, 1H), 2.14 (s, 3H), 2.13 (s, 3H), 1.97 (ddd, *J* = 15.3, 11.1, 4.5 Hz, 1H), 1.83 (qd, *J* = 7.0, 3.0 Hz, 1H), 1.56 (ddd, *J* = 14.4, 11.1, 4.9 Hz, 1H), 1.21 (s, 3H), 1.11-0.96 (m, 31H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 208.6, 208.4, 170.2, 76.7, 76.6, 74.8, 50.0, 39.0, 35.3, 30.1, 29.6, 21.4, 21.1, 17.6 – 17.1 (8C), 13.0, 12.9, 12.8, 12.1, 10.9. **HRMS** (ESI) Exact mass calculated for $C_{26}H_{49}O_7Si_2^+$ $[M+H]^+$: 529.30113, found: 529.30172 and for $C_{26}H_{48}O_7Si_2Na^+$ $[M+Na]^+$: 551.28308, found: 551.28343.

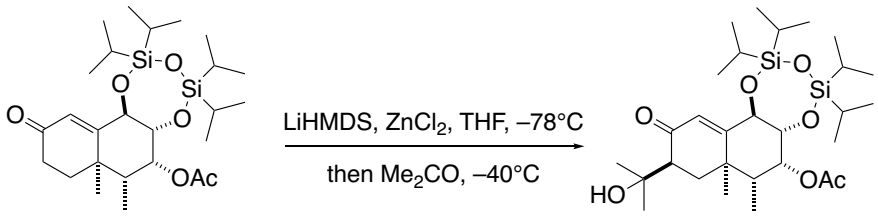


4.27 **4.28**, 68 %

(5a*R*,6*R*,7*R*,7a*R*,11b*R*)-2,2,4,4-Tetraisopropyl-7,7a-dimethyl-10-oxo-5a,6,7,7a,8,9,10,11b-octahydronaphtho[1,2-*f*][1,3,5,2,4]tri-oxadisilepin-6-yl acetate (4.28): A mixture of fully

protected triol **4.27** (64 mg, 0.12 mmol, 1.0 eq.), pyrrolidine (20 µL, 0.24 mmol, 2.0 eq.) and AcOH (14 µL, 0.24 mmol, 2.0 eq.) in toluene (3.5 mL) was stirred at rt for 18 h. The reaction mixture was quenched by addition of a 0.1 M aq. HCl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to afford the octalone **4.28** (42 mg, 82 µmol, 68 %) as a colorless solid.

M.p. = 132.3 – 134.5°C. TLC: $\boldsymbol{R_f}$ = 0.41 (SiO_2, pentane/Et_2O 2:1). **Optical rotation**: $[\alpha]_D^{25}$ = +31.7° (c = 0.31, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2946, 2925, 1751, 1681, 1469, 1228, 1147, 980 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.37 (dd, *J* = 2.1, 0.9 Hz, 1H), 5.40 (t, *J* = 3.3 Hz, 1H), 4.63 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.75 (dd, *J* = 9.6, 3.7 Hz, 1H), 2.48 (ddd, *J* = 17.0, 14.6, 5.0 Hz, 1H), 2.35 (dddd, *J* = 17.0, 4.4, 3.1, 1.0 Hz, 1H), 2.11 (s, 3H), 2.06 (ddd, *J* = 13.4, 5.1, 3.1 Hz, 1H), 1.78 – 1.62 (m, 2H), 1.29 (s, 3H), 1.11 – 0.96 (m, 31H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 199.4, 170.3, 166.9, 123.0, 77.3, 75.2, 72.3, 42.8, 38.7, 37.0, 33.4, 21.2, 19.1, 17.6 – 17.2 (8C), 13.0, 12.9, 12.4, 12.0, 11.0. **HRMS** (ESI) Exact mass calculated for $C_{26}H_{47}O_6Si_2^+$ $[M+H]^+$: 511.29057, found: 511.29098 and for $C_{26}H_{46}O_6Si_2Na^+$ $[M+Na]^+$: 533.27251, found: 533.27276.

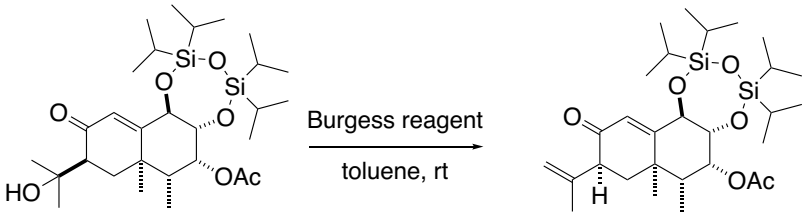


4.28 **4.30**, 67 %

(5a*R*,6*R*,7*R*,7a*R*,9*S*,11b*R*)-9-(2-Hydroxypropan-2-yl)-2,2,4,4-tetraisopropyl-7,7a-dimethyl-10-oxo-5a,6,7,7a,8,9,10,11b-octahydronaphtho[1,2-*f*][1,3,5,2,4]trioxadisilepin-6-yl acetate (4.30): To a solution of octalone **4.28** (5.5 mg, 10.8 µmol, 1.0 eq.) in THF (0.3 mL) at –78°C was added a solution of LiHMDS (1 M in THF, 54 µL, 54 µmol, 5.0 eq.). After 1 h a solution of $ZnCl_2$ (1 M in THF, 22 µL, 22 µmol, 2.0 eq.) was added and the reaction mixture was allowed to warm up to –40°C and stirred for 15 min at this temperature. Freshly distilled acetone (8 µL, 0.11 mmol, 10 eq.) was added and after stirring for 25 min, the reaction mixture was quenched by addition of an aq. tartaric acid solution (5 %). The mixture was extracted with Et_2O (3 x) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered

and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to give the tertiary alcohol **4.30** (4.1 mg, 7.2 µmol, 67 %) as a colorless oil.

TLC: R_f = 0.41 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{22}$ = +40.5° (c = 0.21, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2945, 2868, 1751, 1653, 1464, 1377, 1226, 1125, 887 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.33 (d, *J* = 2.0 Hz, 1H), 5.41 (t, *J* = 3.3 Hz, 1H), 4.97 (brs, 1H), 4.62 (dd, *J* = 9.7, 2.0 Hz, 1H), 3.77 – 3.66 (m, 1H), 2.55 (dd, *J* = 14.6, 4.3 Hz, 1H), 2.12 (s, 3H), 2.03 (dd, *J* = 12.9, 4.4 Hz, 1H), 1.66 (dq, *J* = 7.1, 4.1 Hz, 1H), 1.48 (t, J = 13.8, 1H), 1.32 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.11 – 0.96 (m, 31H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 203.2, 170.2, 167.6, 123.6, 77.0, 75.1, 72.5, 72.2, 50.7, 43.1, 40.0, 39.4, 28.4, 24.9, 21.2, 19.0, 17.6 – 17.2 (8C), 13.0, 12.9, 12.4, 12.0, 11.0. **HRMS** (ESI) Exact mass calculated for $C_{29}H_{53}O_7Si_2^+$ $[M+H]^+$: 569.33243, found: 569.33286. Exact mass calculated for $C_{29}H_{52}O_7Si_2Na^+$ $[M+Na]^+$: 591.31428, found: 591.31437.

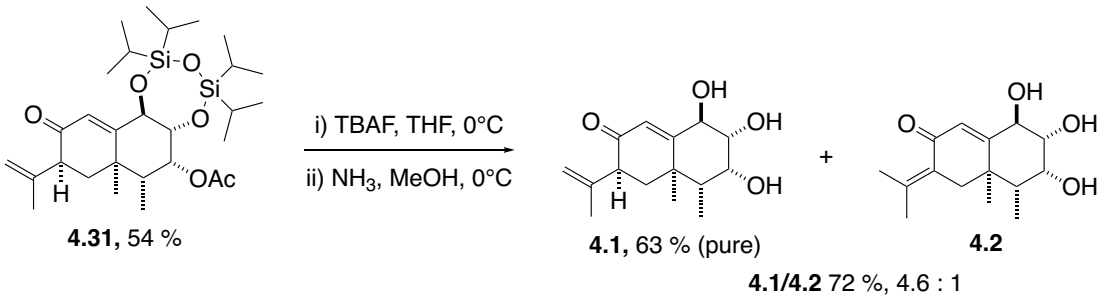


4.30, 67 % **4.31,** 54 %

(5a*R*,6*R*,7*R*,7a*R*,9*S*,11b*R*)-2,2,4,4-Tetraisopropyl-7,7a-dimethyl-10-oxo-9-(prop-1-en-2-yl)-5a,6,7,7a,8,9,10,11b-octahydro-naphtho[1,2-*f*][1,3,5,2,4]trioxadisilepin-6-yl acetate (4.31): Tertiary alcohol **4.30** (18.7 mg, 33 µmol, 1.0 eq.) was dissolved in toluene (0.7 mL) and Burgess reagent (49 mg, 0.20 mmol, 6.1 eq.) was added. The reaction mixture was stirred at rt for 26 h, before it was diluted with H_2O and extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 7:1) to afford the isopropenylated compound **4.31** (9.7 mg, 17.6 µmol, 54 %) as a colorless solid.

M.p. = 108.5 – 112.2°C. TLC: R_f = 0.76 (SiO_2, pentane/Et_2O 3:1). **Optical rotation**: $[\alpha]_D^{25}$ = +86.2° (c = 0.49, $CHCl_3$). **FTIR** (neat): $\tilde{\nu}$ = 2945, 2868, 1751, 1679, 1464, 1229, 1150, 980, 887 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.36 (d, *J* = 2.0 Hz, 1H), 5.41 (t, *J* = 3.3 Hz, 1H), 4.99 (t, *J* = 1.6 Hz, 1H), 4.82 (d, *J* = 1.7 Hz, 1H), 4.63 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.76 (dd, *J* = 9.6, 3.8 Hz, 1H), 3.17 (dd, *J* = 14.4, 4.5 Hz, 1H), 2.12 (s, 3H), 2.00 (dd, *J* = 13.0, 4.6 Hz, 1H), 1.86 (t, *J* = 13.7 Hz, 1H), 1.74 (s, 3H), 1.69 (qd, *J* = 7.0, 3.0 Hz, 1H), 1.35 (s, 3H), 1.12 –

0.95 (m, 31H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 198.7, 170.2, 165.8, 143.4, 123.1, 114.5, 77.1, 75.3, 72.2, 50.2, 43.2, 42.9, 39.3, 21.2, 20.3, 19.1, 17.6 – 17.2 (8C), 13.0, 12.9, 12.3, 12.0, 11.0. **HRMS** (ESI) Exact mass calculated for $C_{29}H_{51}O_6Si_2^+$ $[M+H]^+$: 551.32187, found: 551.32224.

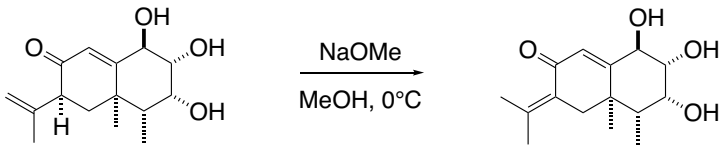


Guignarderemophilane C (4.1): The fully protected triol **4.31** (10 mg, 18 µmol, 1.0 eq.) was dissolved in THF (0.35 mL) and cooled to 0°C. A solution of TBAF (1 M in THF, 73 µL, 73 µmol, 4.0 eq.) was added and the reaction mixture was stirred at 0°C for 50 min, before it was treated with sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was dissolved in a solution of NH_3 (7 M in MeOH, 0.35 mL) and stirred at rt for 2 h. The solvent was evaporated (at 30°C bath temperature) and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH 12:1) to afford a 4.6:1 mixture of guignarderemophilane C and D (3.5 mg, 13.1 µmol, 72 % over two steps). For analytical purposes, the mixture of **4.1** and **4.2** was purified by semi-preparative HPLC using the conditions given below. The residue was dissolved in a mixture of H_2O/MeCN/MeOH (10:4:1, 0.8 mL) and in total eight runs had to be carried out with injection of 100 µL of the sample per run. Two fractions were collected from 18.00 to 19.20 min (fraction 1), and from 19.20 to 21.00 min (fraction 2), respectively. The first fraction gave pure guignarderemophilane C (2.2 mg, 63 %) and the second fraction gave a 1:1 mixture of guignarderemophilanes C and D (1.1 mg, 31 %) after concentration by rotary evaporator and lyophilizer.

Column: Synergi Hydro-RP 10 µm 80 Å, 150 mm x 10.0 mm; solvent A: H_2O; solvent B: MeCN; flow = 4.6 mL/min; T = rt; UV detection at 222 nm; solvent system: isocratic, [B] = 18 %.

TLC: $\mathbf{R}_f$ = 0.43 (SiO_2, CH_2Cl_2/MeOH 12:1) **Optical rotation**: $[\alpha]_D^{27}$ = +35.0° (c = 0.88, MeOH). **FTIR** (neat): $\tilde{\nu}$ = 3401, 2968, 2940, 2881, 1662, 1443, 1327, 1132, 1101, 1079, 889 cm^{-1}. **^{1}H NMR** (500 MHz, MeOD) δ = 6.20 (d, *J* = 2.0 Hz, 1H), 4.93 (t, *J* = 1.7 Hz, 1H), 4.82

– 4.80 (m, 1H), 4.48 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.86 (t, *J* = 3.0 Hz, 1H), 3.38 (dd, *J* = 10.4, 3.3 Hz, 1H), 3.24 (dd, *J* = 14.4, 4.6 Hz, 1H), 1.99 (dd, *J* = 13.0, 4.6 Hz, 1H), 1.88 (t, *J* = 13.7 Hz, 1H), 1.70 (t, *J* = 1.0 Hz, 3H), 1.51 (qd, *J* = 7.1, 2.8 Hz, 1H), 1.41 (s, 3H), 1.14 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, MeOD) δ = 201.7, 172.6, 144.9, 122.0, 114.7, 77.4, 75.6, 70.1, 51.3, 45.9, 44.4, 40.8, 20.2, 19.8, 11.8. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{22}O_4Na^+$ $[M+Na]^+$: 289.14103, found: 289.14085.



4.1 **4.2**, 70 %

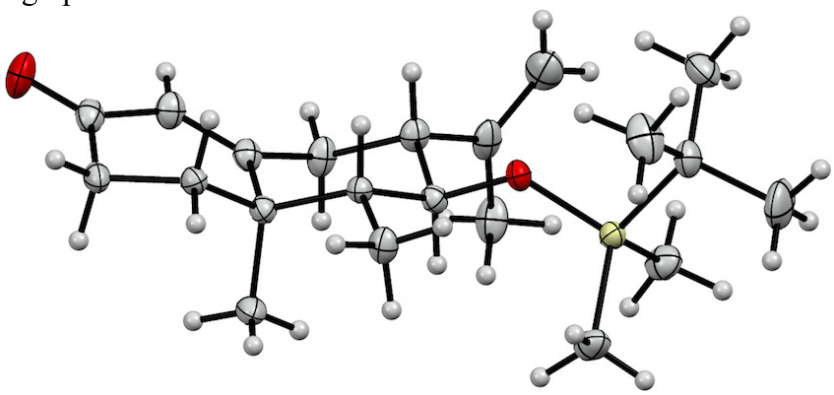
Guignarderemophilane D (4.2): A solution of **4.1** (2.0 mg, 7.5 µmol, 1.0 equiv.) in NaOMe (0.5 M in MeOH, 1.0 mL) was stirred for 6 h at 0°C. The reaction was quenched by addition of sat. aq. NH_4Cl solution and the resulting turbid mixture was extracted with EtOAc (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was subjected to flash column chromatography (CH_2Cl_2/MeOH 14:1) to give guignarderemophilane D (1.4 mg, 5.3 µmol, 70 %) as a colorless solid.

TLC: $\mathbf{R_f}$ = 0.23 (SiO_2, CH_2Cl_2/MeOH 14:1) **Optical rotation**: $[\alpha]_D^{25}$ = +38.2° (c = 0.70, MeOH). **FTIR** (neat): $\tilde{\nu}$ = 3401, 2965, 2882, 1652, 1626, 1370, 1297, 1072, 1017 cm^{-1}. **^{1}H NMR** (500 MHz, MeOD) δ = 6.20 (d, *J* = 2.2 Hz, 1H), 4.44 (dd, *J* = 10.4, 2.2 Hz, 1H), 3.86 (t, *J* = 2.9 Hz, 1H), 3.39 (dd, *J* = 10.3, 3.2 Hz, 1H), 2.98 (d, *J* = 13.6 Hz, 1H), 2.12 (d, *J* = 14.3 Hz, 1H), 2.08 (d, *J* = 2.1 Hz, 3H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.56 (qd, *J* = 7.1, 2.7 Hz, 1H), 1.18 (d, J = 1.4 Hz, 3H), 1.17 (s, 3H). **^{13}C NMR** (126 MHz, MeOD) δ = (126 MHz, MeOD) δ = 194.2, 171.3, 145.6, 128.6, 124.2, 77.5, 75.6, 70.1, 44.7, 43.6, 43.1, 22.8, 22.4, 20.1, 12.1. **HRMS** (ESI) Exact mass calculated for $C_{15}H_{23}O_4^+$ $[M+H]^+$: 267.15909, found: 267.15899 and $C_{15}H_{22}O_4Na^+$ $[M+Na]^+$: 289.14075, found: 289.14084.

7 APPENDICES

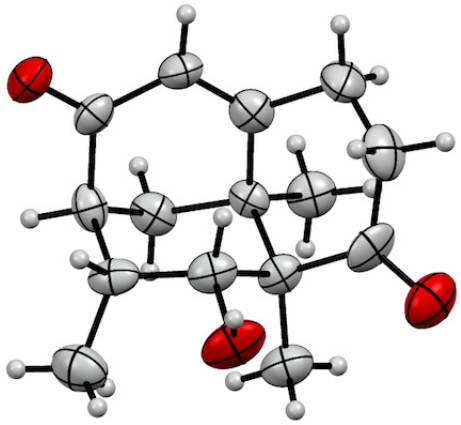
7.1 Crystal Structures

X-Ray Crystallographic Data for **2.42**



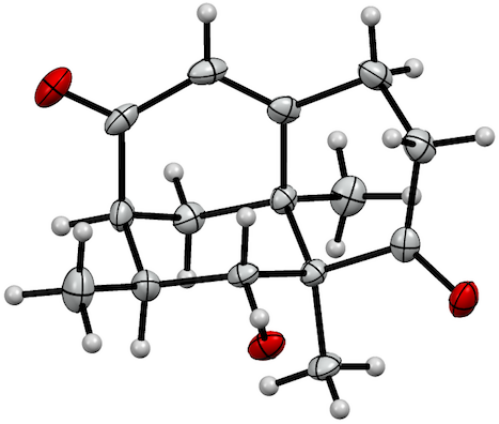
Empirical formula		$C_{21}H_{36}O_2Si$
Formula weight [g mol^{-1}]		348.60
Crystal color, habit		colorless, needle
Crystal dimensions [mm]		0.02 x 0.09 x 0.33
Temperature [K]		100
Radiation, λ [Å]		Cu K_α, 1.54178
Crystal system		monoclinic
Space group		$P2_1$
Z		2
Reflections for cell determination		9949
2Θ range for cell determination [°]		6 – 136
Unit cell parameters	a [Å]	10.8142(2)
	b [Å]	6.39970(10)
	c [Å]	15.9412(3)
	α [°]	90
	β [°]	105.1560(10)
	γ [°]	90
	V [Å^3]	1064.88(2)
$F(000)$		384
D_x [g cm^{-3}]		1.087
μ(Cu K_α) [mm^{-1}]		1.031
$2\Theta_{(max)}$ [°]		136.0
Total reflections measured		21476
Symmetry independent reflections		3788
R_{int}		0.039
Reflections with $I > 2\sigma(I)$		3610
Reflections used in refinement		3545
Parameters refined; restraints		246; 464
Final	$R(F)$ [$I > 2\sigma(I)$ reflections]	0.0291
	$wR(F^2)$ (all data)	0.0322
Goodness of fit		1.0961
Final Δ_{max}/σ		0.002
$\Delta\rho$ (max; min) [e Å^{-3}]		0.24; -0.19
$\sigma(d_{(C\text{-}C)})$ [Å]		0.003 – 0.17

X-Ray Crystallographic Data for 11*R*-**2.70**



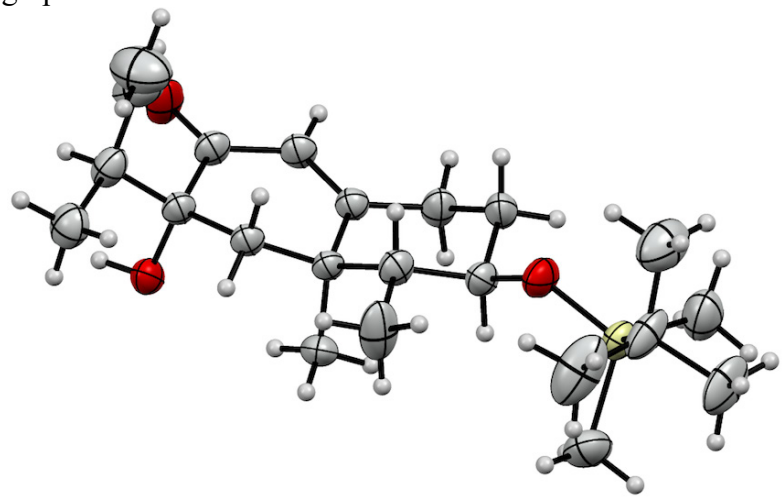
Empirical formula		$C_{15}H_{20}O_3$
Formula weight [g mol^{-1}]		248.32
Crystal color, habit		colorless, plate
Crystal dimensions [mm]		0.02 x 0.11 x 0.20
Temperature [K]		123
Radiation, λ [Å]		Cu K_α, 1.54178
Crystal system		monoclinic
Space group		$P2_1$
Z		4
Reflections for cell determination		6584
2Θ range for cell determination [°]		6 – 136
Unit cell parameters	a [Å]	7.9901(5)
	b [Å]	11.0438(7)
	c [Å]	14.7165(9)
	α [°]	90
	β [°]	99.899(4)
	γ [°]	90
	V [Å^3]	1279.27(8)
F(000)		536
D_x [g cm^{-3}]		1.289
μ(Cu K_α) [mm^{-1}]		0.711
2$\Theta_{(max)}$ [°]		136.0
Total reflections measured		17596
Symmetry independent reflections		4636
R_{int}		0.034
Reflections with $I > 2\sigma(I)$		4047
Reflections used in refinement		3785
Parameters refined; restraints		332; 3
Final	$R(F)$ [$I > 2\sigma(I)$ reflections]	0.0615
	$wR(F^2)$ (all data)	0.0454
Goodness of fit		0.898
Final Δ_{max}/σ		0.000
$\Delta\rho$ (max; min) [e Å^{-3}]		0.30; -0.19

X-Ray Crystallographic Data for 11*S*-**2.70**



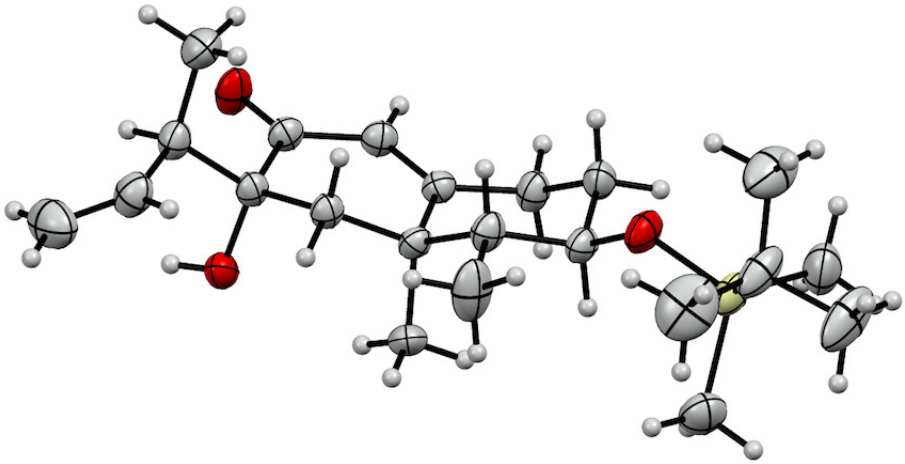
Empirical formula		$C_{15}H_{20}O_3$
Formula weight [g mol^{-1}]		248.32
Crystal color, habit		colorless, plate
Crystal dimensions [mm]		0.02 x 0.11 x 0.21
Temperature [K]		123
Radiation, λ [Å]		Cu K_α, 1.54178
Crystal system		orthorhombic
Space group		$P2_12_12_1$
Z		8
Reflections for cell determination		8502
2Θ range for cell determination [°]		10 – 138
Unit cell parameters	a [Å]	8.4759(3)
	b [Å]	11.9984(5)
	c [Å]	25.2108(10)
	α [°]	90
	β [°]	90
	γ [°]	90
	V [Å^3]	2563.87(10)
$F(000)$		1072
D_x [g cm^{-3}]		1.287
μ(Cu K_α) [mm^{-1}]		0.709
$2\Theta_{(max)}$ [°]		138.0
Total reflections measured		19355
Symmetry independent reflections		4556
R_{int}		0.030
Reflections with $I > 2\sigma(I)$		4328
Reflections used in refinement		4244
Parameters refined; restraints		332; 2
Final	$R(F)$ [$I > 2\sigma(I)$ reflections]	0.0324
	$wR(F^2)$ (all data)	0.0288
Goodness of fit		0.9542
Final Δ_{max}/σ		0.001
$\Delta\rho$ (max; min) [e Å^{-3}]		0.36; -0.19

X-Ray Crystallographic Data for 11*S*-**2.80**



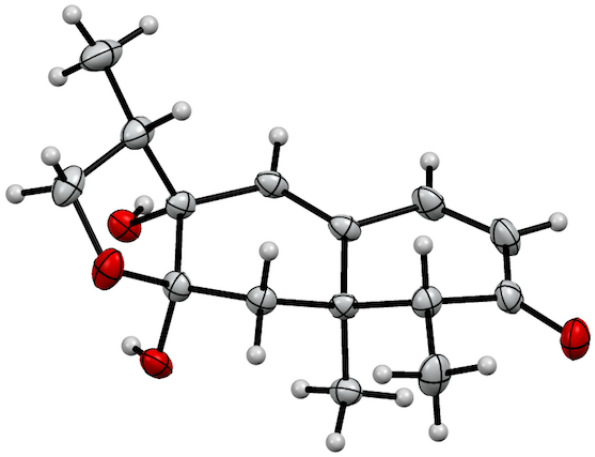
Crystallized from		hexane / Et_2O
Empirical formula		$C_{22}H_{38}O_3Si$
Formula weight [g mol^{-1}]		378.61
Crystal color, habit		colorless, needle
Crystal dimensions [mm]		0.02 x 0.07 x 0.28
Temperature [K]		160(1)
Radiation, λ [Å]		Cu K_α, 1.54184
Crystal system		monoclinic
Space group		*C*2
Z		4
Reflections for cell determination		6505
2Θ range for cell determination [°]		6 – 146
Unit cell parameters	*a* [Å]	26.0154(6)
	b [Å]	7.2638(2)
	c [Å]	12.3046(3)
	α [°]	90
	β [°]	94.652(2)
	γ [°]	90
	V [Å^3]	2317.55(10)
F(000)		832
D_x [g cm^{-3}]		1.085
μ(Cu K_α) [mm^{-1}]		1.016
Scan type		ω
2$\Theta_{(max)}$ [°]		146.0
Transmission factors (min; max)		0.719; 1.000
Total reflections measured		11650
Symmetry independent reflections		4492
R_{int}		0.034
Reflections with $I > 2\sigma(I)$		4050
Reflections used in refinement		4487
Parameters refined; restraints		287; 50
Final	*R*(*F*) [$I > 2\sigma(I)$ reflections]	0.0398
	wR(F^2) (all data)	0.1105
Goodness of fit		1.069
Final Δ_{max}/σ		0.000
$\Delta\rho$ (max; min) [e Å^{-3}]		0.18; -0.19
$\sigma(d_{(C\text{-}C)})$ [Å]		0.003 – 0.011

X-Ray Crystallographic Data for 11*R*-**2.80**



Crystallized from		hexane / Et_2O
Empirical formula		$C_{22}H_{38}O_3Si$
Formula weight [g mol^{-1}]		378.61
Crystal color, habit		colorless, needle
Crystal dimensions [mm]		0.02 x 0.07 x 0.26
Temperature [K]		160(1)
Radiation, λ [Å]		Cu K_α, 1.54184
Crystal system		monoclinic
Space group		*C*2
Z		4
Reflections for cell determination		5160
2Θ range for cell determination [°]		7 – 147
Unit cell parameters	*a* [Å]	25.2644(6)
	b [Å]	7.33538(18)
	c [Å]	12.3638(3)
	α [°]	90
	β [°]	94.354(2)
	γ [°]	90
	V [Å^3]	2284
F(000)		832
D_x [g cm^{-3}]		1.101
μ(Cu K_α) [mm^{-1}]		1.030
Scan type		ω
2$\Theta_{(max)}$ [°]		148.2
Transmission factors (min; max)		0.732; 1.000
Total reflections measured		11790
Symmetry independent reflections		4406
R_{int}		0.031
Reflections with $I > 2\sigma(I)$		4108
Reflections used in refinement		4406
Parameters refined; restraints		287; 50
Final	*R*(*F*) [$I > 2\sigma(I)$ reflections]	0.0440
	wR(F^2) (all data)	0.1229
Goodness of fit		1.029
Final Δ_{max}/σ		0.000
$\Delta\rho$ (max; min) [e Å^{-3}]		0.64; -0.21
$\sigma(d_{(C\text{-}C)})$ [Å]		0.004 – 0.012

X-ray Crystallographic Data for **3.11**



Crystallized from		CH_2Cl_2 / pentane
Empirical formula		$C_{15}H_{20}O_4$
Formula weight [g mol^{-1}]		264.31
Crystal color, habit		colorless, plate
Crystal dimensions [mm]		0.01 x 0.25 x 0.28
Temperature [K]		160(1)
Radiation, λ [Å]		Cu K_α, 1.54184
Crystal system		orthorhombic
Space group		$P2_12_12_1$ (#19)
Z		8
Reflections for cell determination		27539
2Θ range for cell determination [°]		7 – 149
Unit cell parameters	a [Å]	7.26111(5)
	b [Å]	12.04626(11)
	c [Å]	31.0465(3)
	α [°]	90
	β [°]	90
	γ [°]	90
	V [Å^3]	2715.61(4)
F(000)		1136
D_x [g cm^{-3}]		1.293
μ(Cu K_α) [mm^{-1}]		0.759
Scan type		ω
2$\Theta_{(max)}$ [°]		148.4
Transmission factors (min; max)		0.656; 1.000
Total reflections measured		51176
Symmetry independent reflections		5446
R_{int}		0.036
Reflections with $I > 2\sigma(I)$		5305
Reflections used in refinement		5445
Parameters refined; restraints		365
Final	$R(F)$ [$I > 2\sigma(I)$ reflections]	0.0286
	$wR(F^2)$ (all data)	0.0724
Goodness of fit		1.060
Final Δ_{max}/σ		0.001
$\Delta\rho$ (max; min) [e Å^{-3}]		0.22; -0.16
$\sigma(d_{(C-C)})$ [Å]		0.002 – 0.003

7.2 ^{1}H and ^{13}C NMR Spectra

^{1}H and ^{13}C NMR spectra for all the characterized compounds are given at the end of this thesis.

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10 CURRICULUM VITAE

Raphael Adrian Liffert, born May 30, 1986 in Lucerne, Switzerland

EDUCATION AND PROFESSIONAL EXPERIENCE

09/2013 – 07/2018 **Dissertation at the University of Basel and (from 08/2015) University of Zurich:** PhD thesis in organic chemistry under the supervision of Prof. Dr. Karl Gademann: *Total Syntheses of Eremophilane Sesquiterpenoids Based on Biogenetic Hypotheses*

01/2013 – 07/2013 **Internship at Novartis Institutes for BioMedical Research (NIBR), Novartis Pharma AG in Basel**

08/2011 – 11/2012 **Master of Science in Chemistry at the University of Basel:** master thesis in organic chemistry under the supervision of Prof. Dr. Karl Gademann: *Semi-Synthetic Studies on the Neuritogenic Steroid Withanolide A*

09/2008 – 07/2011 **Bachelor of Science in Chemistry at the University of Basel**

08/2007 – 08/2008 **Full-time accountant at CONCORDIA Swiss Health and Accident Insurance Ltd in Lucerne**

08/1999 – 06/2007 **Secondary Education (high school) at the Kantonsschule Reussbühl in Lucerne:** focus subjects: chemistry, biology

PUBLICATIONS

R. Liffert, A. Ilazi, K. Gademann "Total Synthesis of the Polyoxygenated Sesquiterpenes Guignarderemophilanes C and D" *Helv. Chim. Acta* **2018**, doi: 10.1002/hlca.201800011.

R. Liffert, A. Linden, K. Gademann "Total Synthesis of the Sesquiterpenoid Periconianone A Based on a Postulated Biogenesis" *J. Am. Chem. Soc.* **2017**, *139*, 16096–16099. Highlighted in *Synfacts* **2018**, *14*, 119 and *CHIMIA* (Swiss Science Concentrates) **2018**, *72*, 151.

R. Liffert, K. Gademann "Mapping Out Biogenetic Hypotheses by Chemical Synthesis" *CHIMIA* **2017**, *71*, 841–844.

J. Gomes, C. Daeppen, R. Liffert, J. Roesslein, E. Kaufmann, A. Heikinheimo, M. Neuburger, K. Gademann "Formal Total Synthesis of (−)-Jiadifenolide and Synthetic Studies toward Seco-Prezizaane-Type Sesquiterpenes" *J. Org. Chem.* **2016**, *81*, 11017–11034.

R. Liffert, J. Hoecker, C. K. Jana, T. M. Woods, P. Burch, H. J. Jessen, M. Neuburger, K. Gademann "Withanolide A: Synthesis and Structural Requirements for Neurite Outgrowth" *Chem. Sci.* **2013**, *4*, 2851–2857.

J. Hoecker, R. Liffert, P. Burch, R. Wehlauch, K. Gademann "Caged Retinoids as Photoinducible Activators: Implications for Cell Differentiation and Neurite Outgrowth" *Org. Biomol. Chem.* **2013**, *11*, 3314–3321.

CONFERENCES AND AWARDS

POSTER PRESENTATIONS

Enantioselective Total Synthesis of Periconianone A

ECHC 2016 - XXVII European Colloquium on Heterocyclic Chemistry, Amsterdam, **2016**
Dorothy Crowfoot Hodgkin Symposium, Zürich, **2016**
Doktorandentag, Zürich, **2017**, best poster award
Swiss Summer School, Villars-sur-Ollon, **2017**, 1st prize poster award
SCS - Syngenta Symposium, Stein, **2017**

ORAL PRESENTATION

Enantioselective Total Synthesis of Periconianone A

Chemistry Meets Industry Event for PhD Students, Lonza Group AG*,* Visp, **2017**

TEACHING EXPERIENCE

02/2017 – 12/2017 supervision of the master thesis *Furan Shuffling – Biogenetic Relation between Microsphaeropsisin B and Periconianone C* via *an α-Ketol Rearrangement*, University of Zurich

01/2016 – 12/2017 instruction of an apprentice, University of Zurich

02/2016 – 08/2016 supervision of the master thesis *Enantioselective Total Synthesis of Guignarderemophilanes C and D*, University of Zurich

04/2016 – 06/2016 lab course assistant for *Practical Course in Organic Chemistry I*, University of Zurich

02/2015 – 05/2015 lab course assistant for *Advanced Organic Chemistry*, University of Basel

06/2014 – 09/2014 lab course assistant for *Organic Chemistry Practicum for Biologists and Pharmacists*, University of Basel

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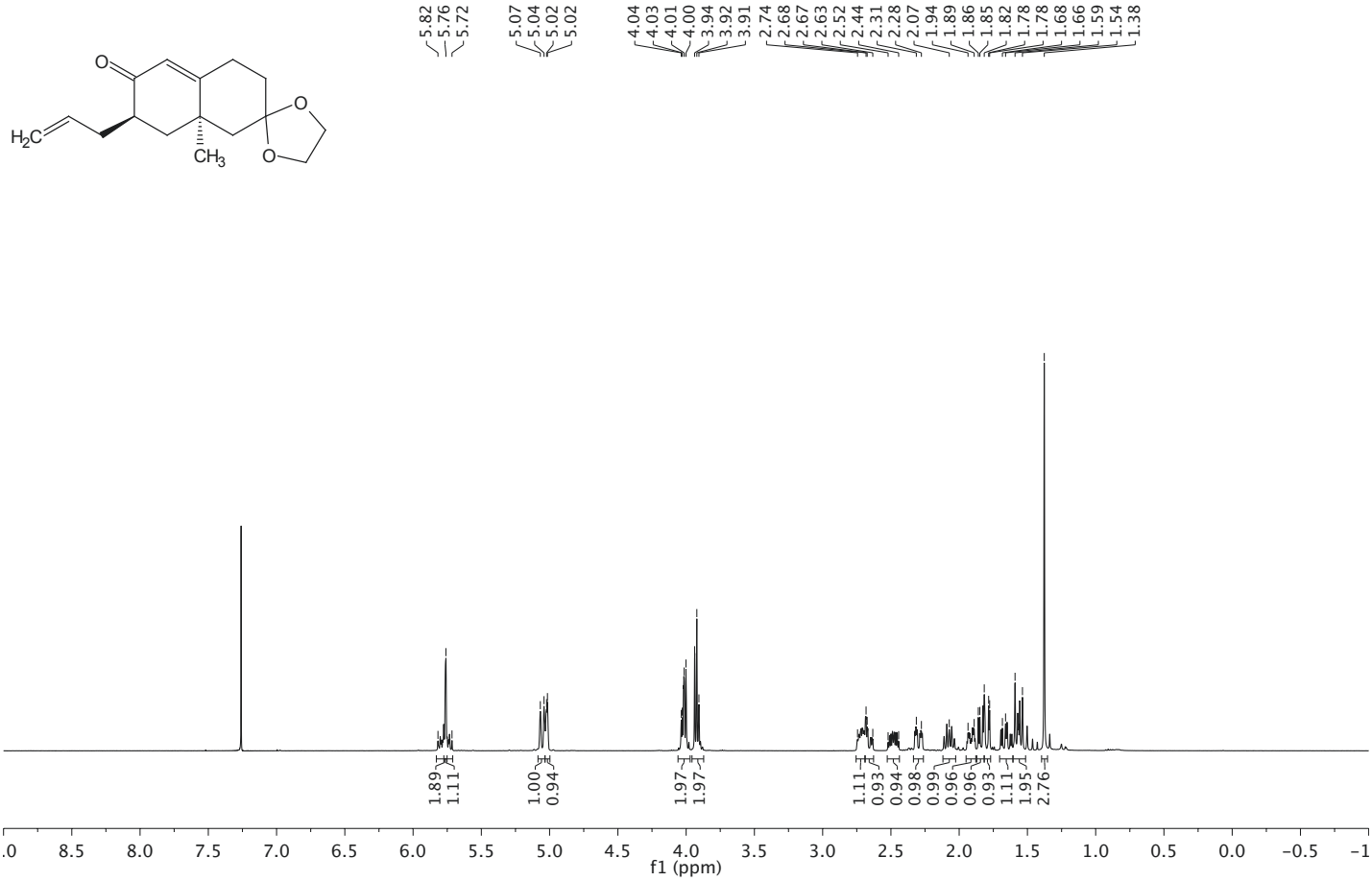

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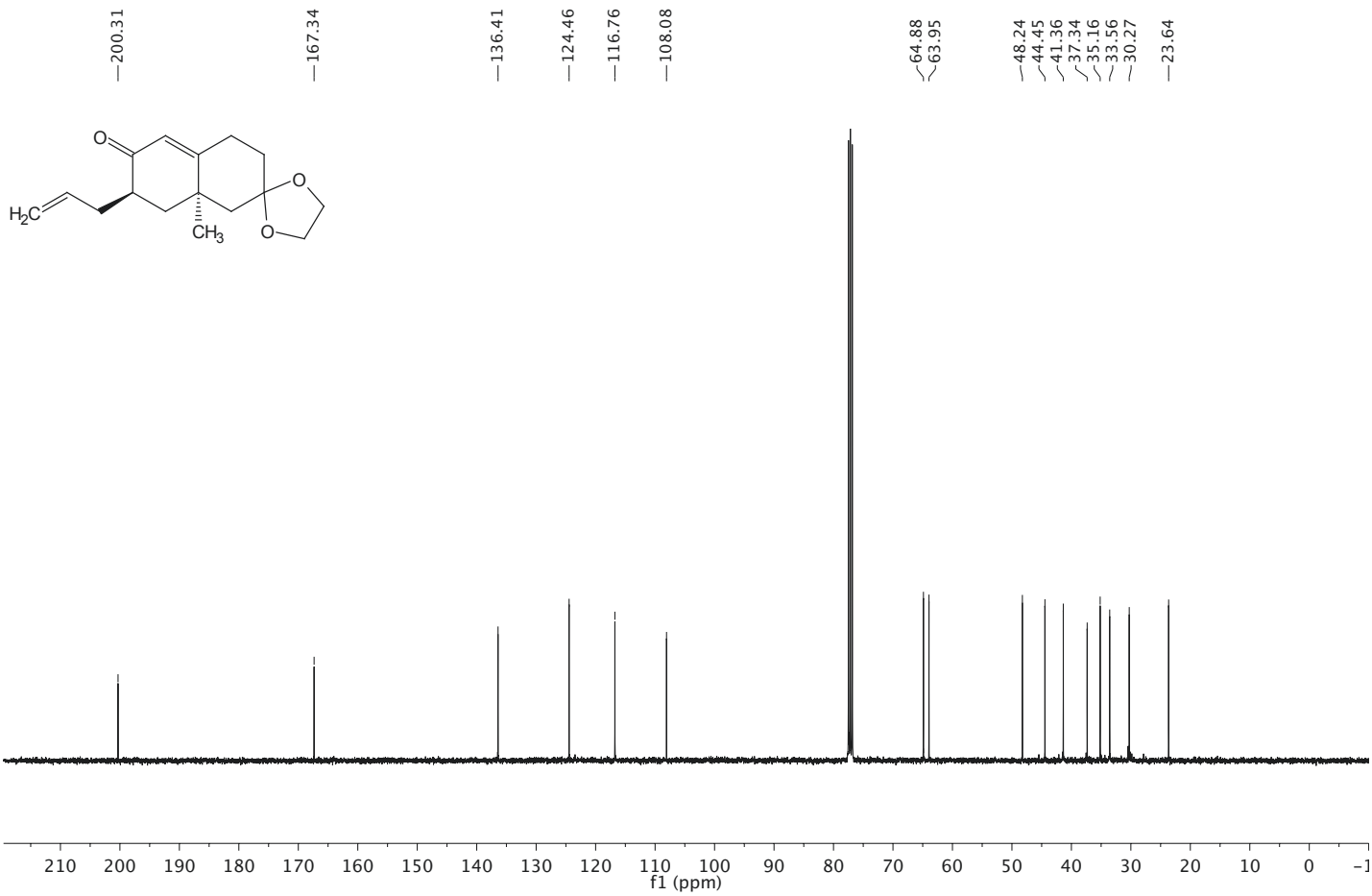

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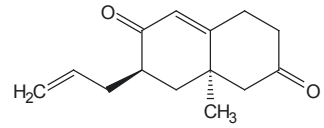

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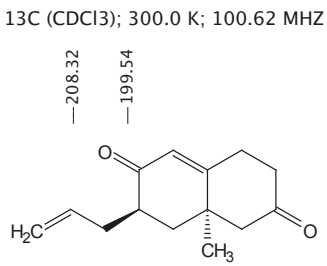

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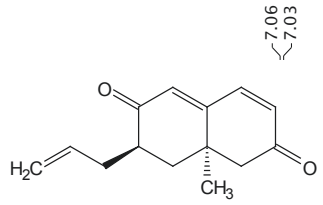

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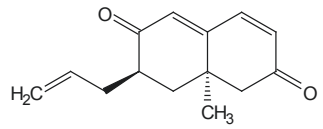

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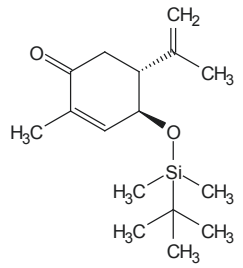

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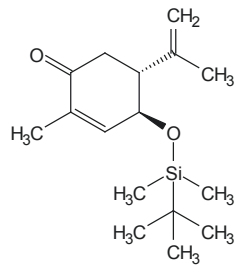

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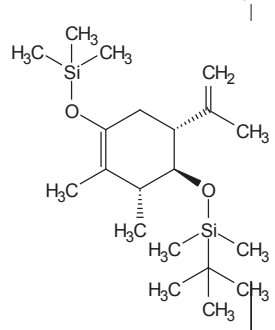

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4.80
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3.45
2.40
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2.19
2.12
2.09
1.99
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1.52
1.07
1.06
0.86
0.16
0.07
0.04

2.06 1.00 0.99 1.21 2.09 3.06 3.19 2.94 9.50 8.76 2.77 3.02

f1 (ppm)

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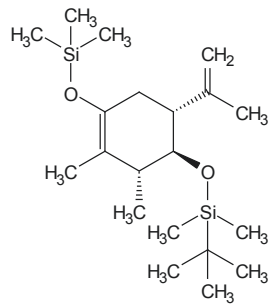

146.43
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77.16 CDCl3
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26.22
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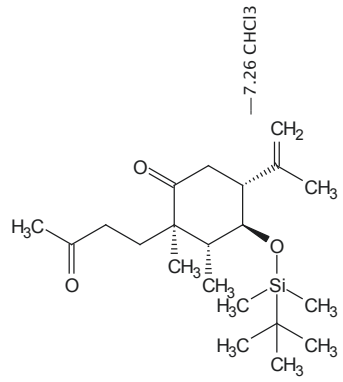
f1 (ppm)

1H (CDCl3); 295.0 K; 500.13 MHZ



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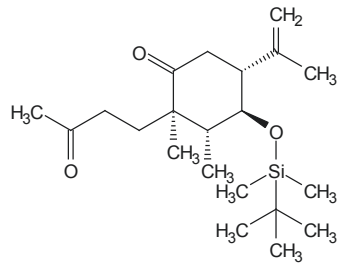
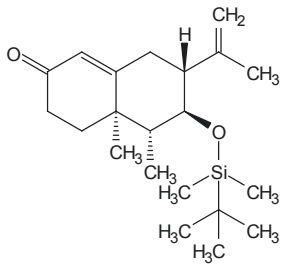


1H (CDCl3); 295.0 K; 500.13 MHZ

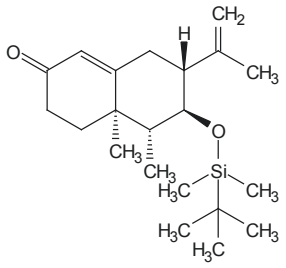


5.75 | 4.85 4.85 | 3.56 | 2.48 2.48 2.39 2.37 2.35 2.24 2.17 2.07 2.02 1.76 1.73 1.69 1.43 1.40 1.14 1.02 1.00 0.87 | 0.05 0.01

1.03 2.17 1.04 1.10 1.99 2.17 1.10 4.49 1.16 3.26 3.41 10.23 3.32 3.32

f1 (ppm)

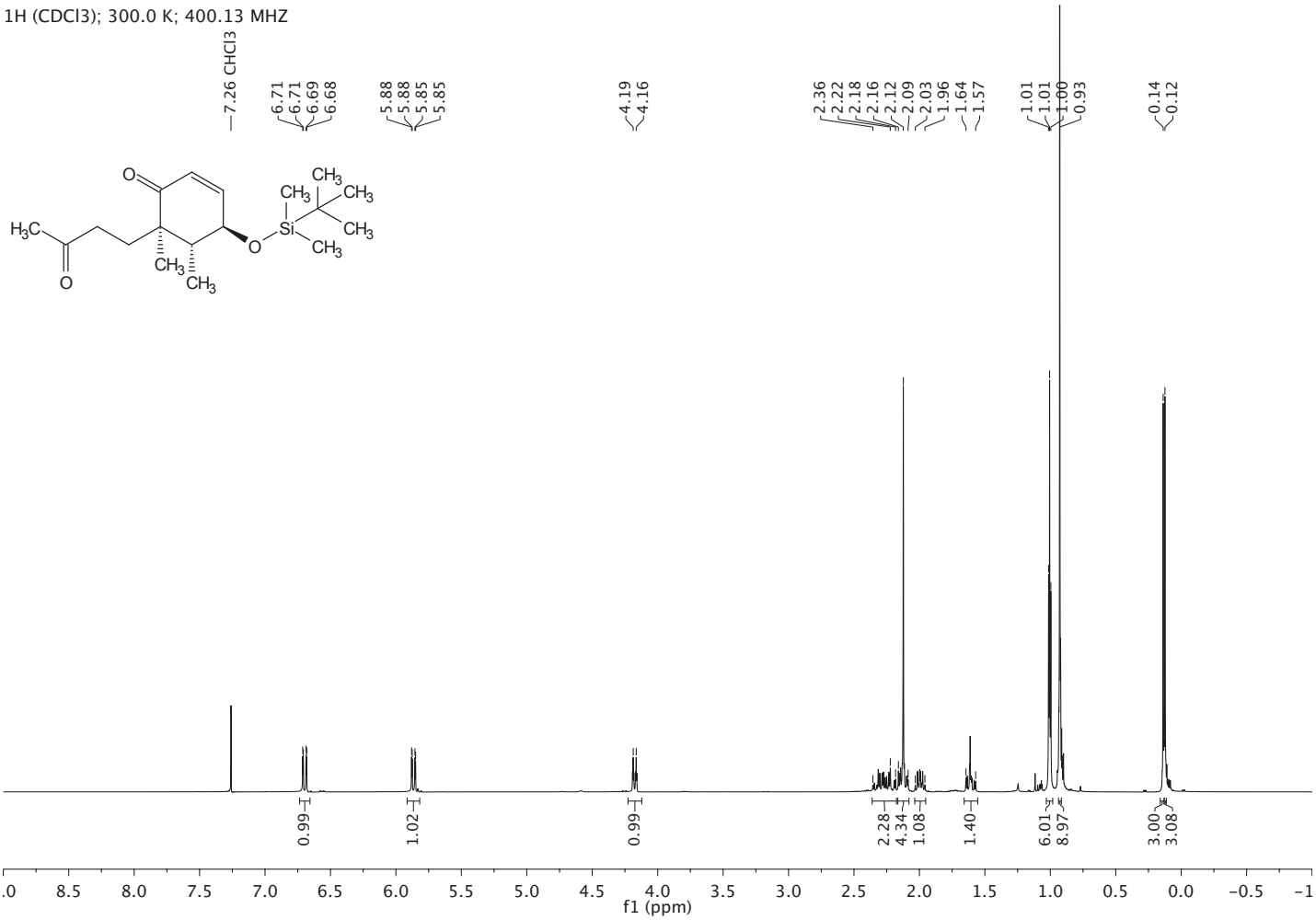
13C (CDCl3); 296.8 K; 100.62 MHZ



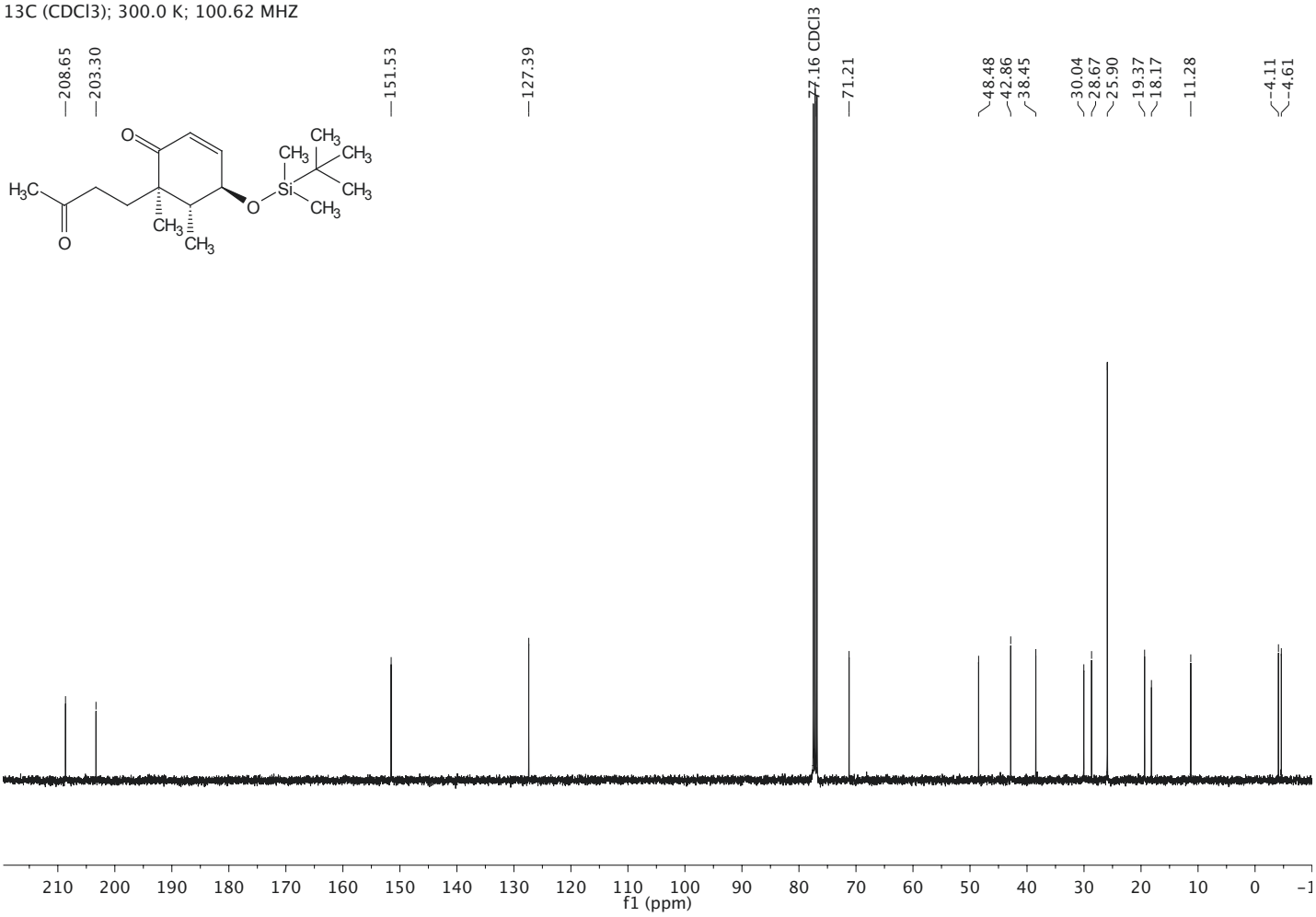
199.46 | 169.13 | 145.51 | 124.12 | 114.03 | 74.39 | 54.09 | 50.33 | 39.41 37.36 36.08 33.61 | 26.37 20.79 18.61 17.61 11.98 | -2.81 -3.34

f1 (ppm)

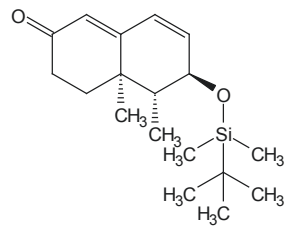
1H (CDCl3); 300.0 K; 400.13 MHZ



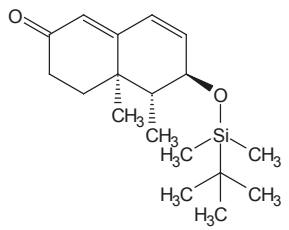
13C (CDCl3); 300.0 K; 100.62 MHZ



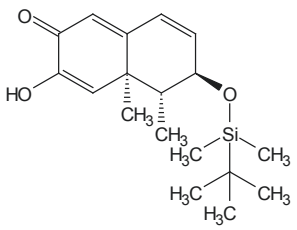
1H (CDCl3); 300.0 K; 400.13 MHZ



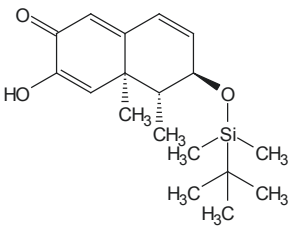
13C (CDCl3); 300.0 K; 100.62 MHZ



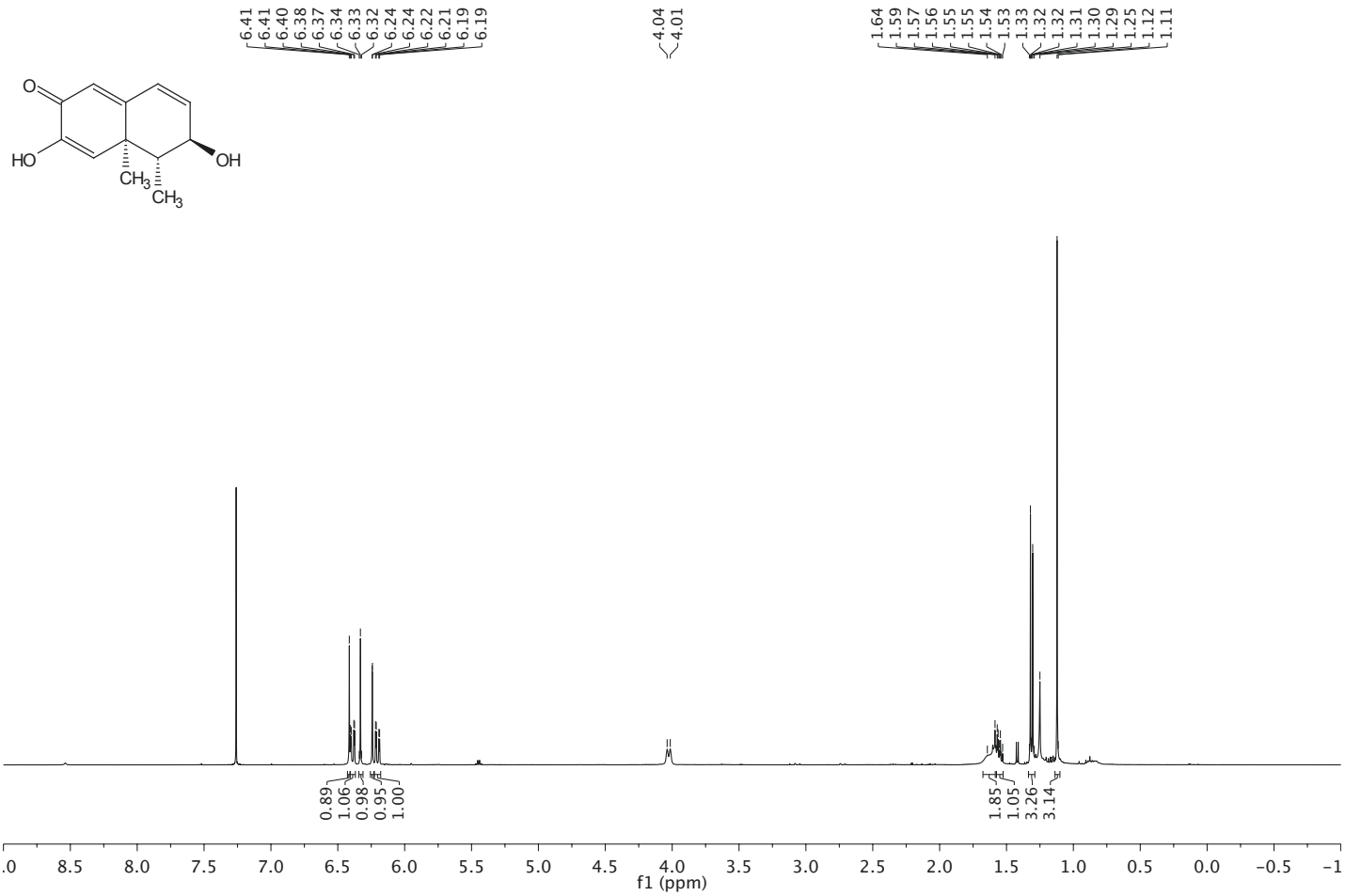
1H (CDCl3); 300.0 K; 400.13 MHZ



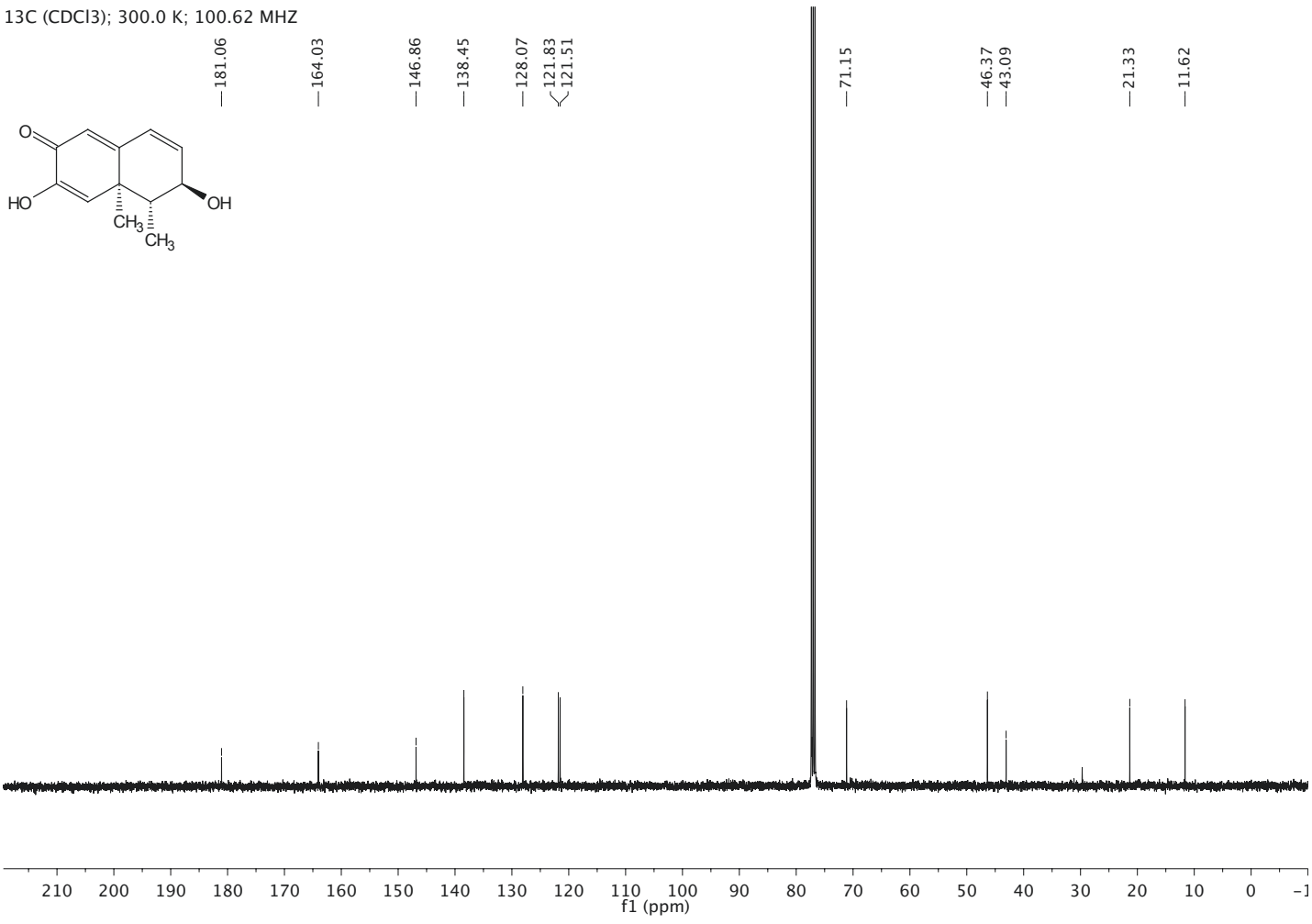
13C (CDCl3); 300.0 K; 100.62 MHZ



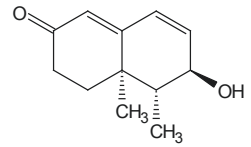
1H (CDCl3); 300.0 K; 400.13 MHZ



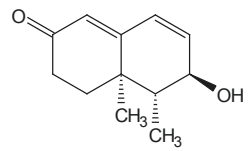
13C (CDCl3); 300.0 K; 100.62 MHZ



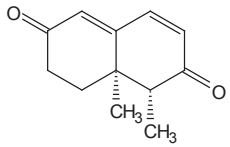
1H (CDCl3); 298.0 K; 500.25 MHZ



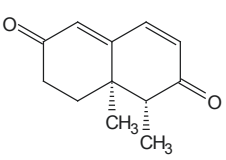
13C (CDCl3); 298.0 K; 125.80 MHZ



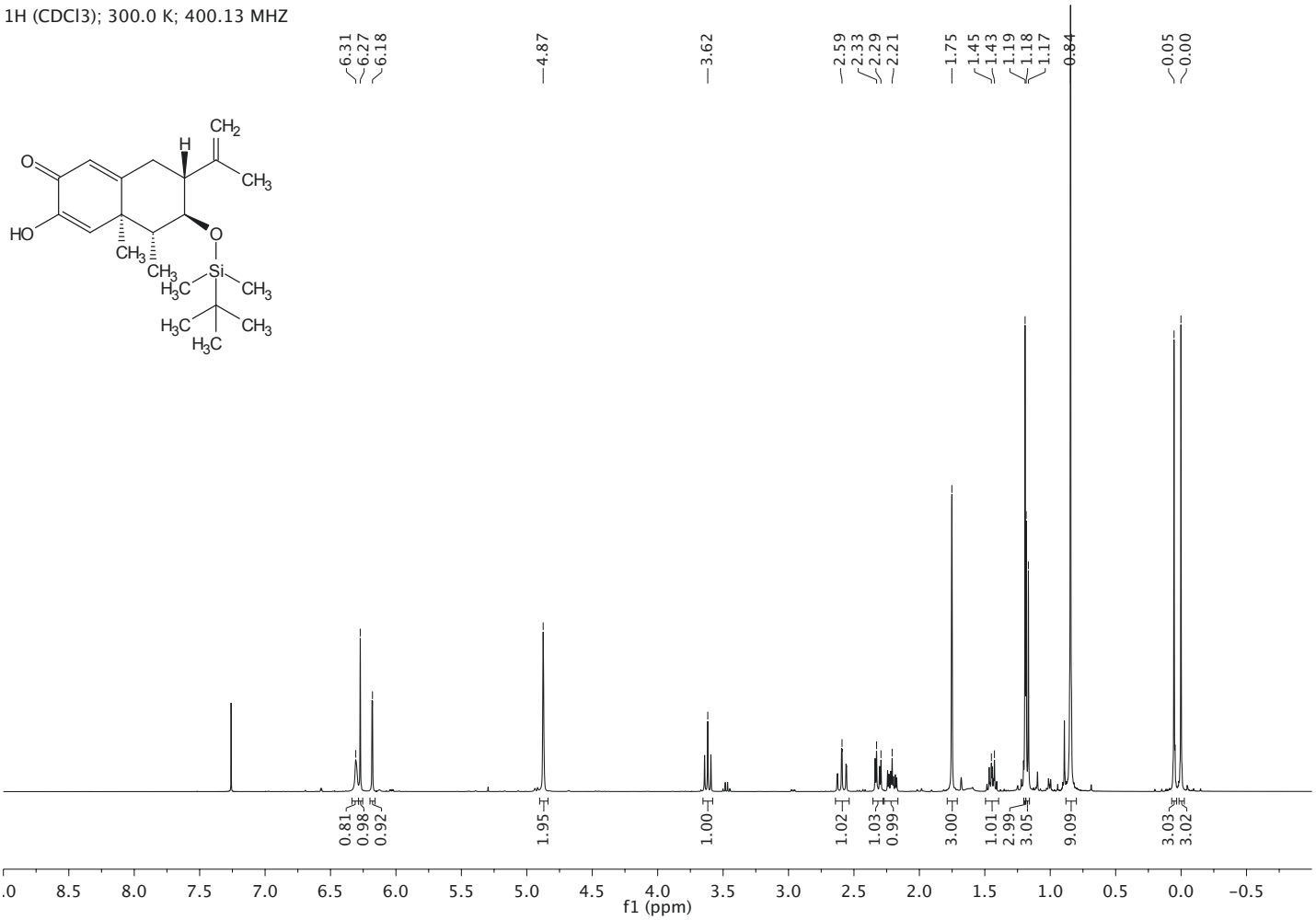
1H (CDCl3); 298.0 K; 500.25 MHZ



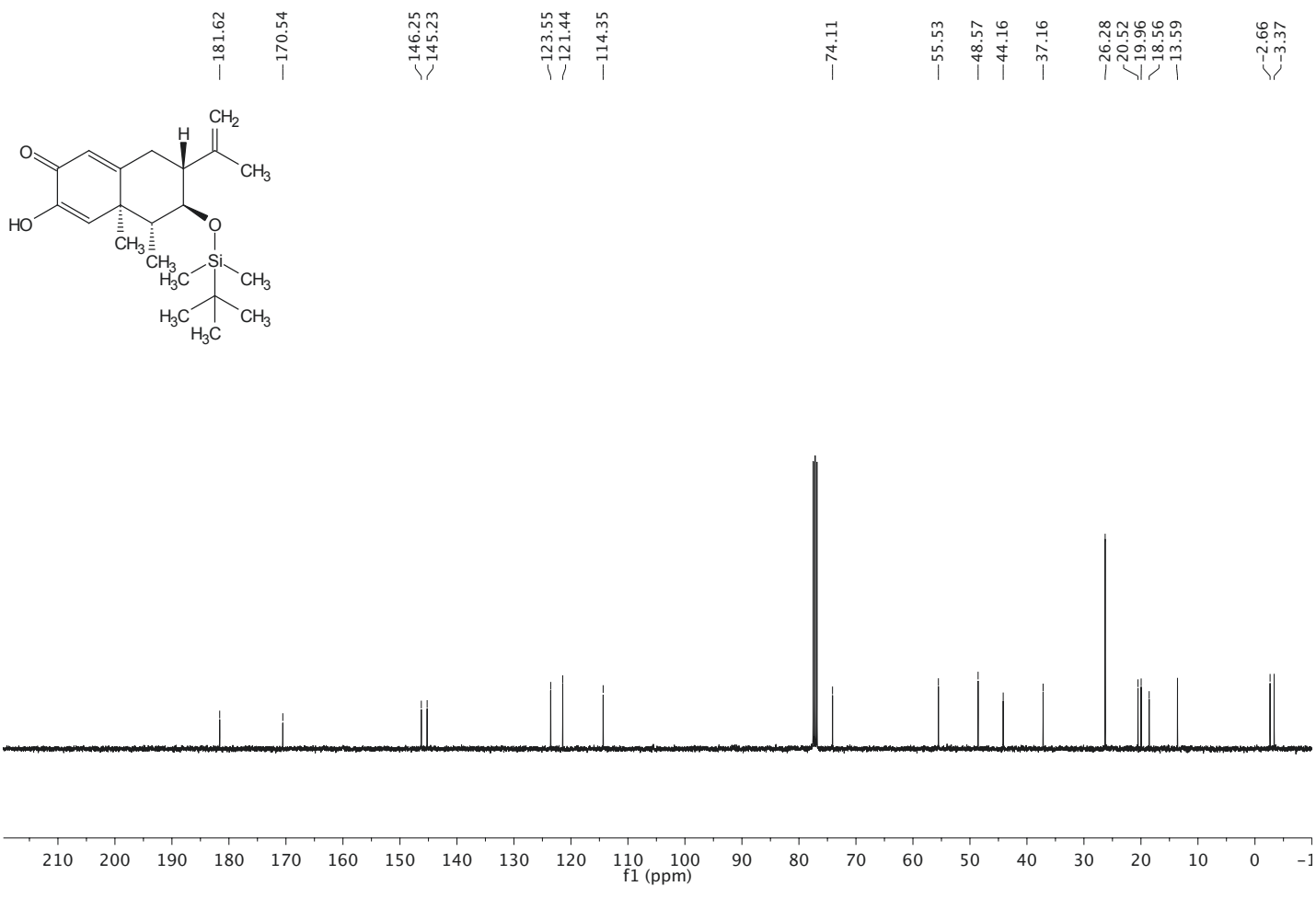
13C (CDCl3); 298.0 K; 125.80 MHZ



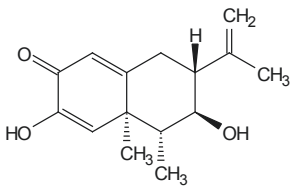
1H (CDCl3); 300.0 K; 400.13 MHZ

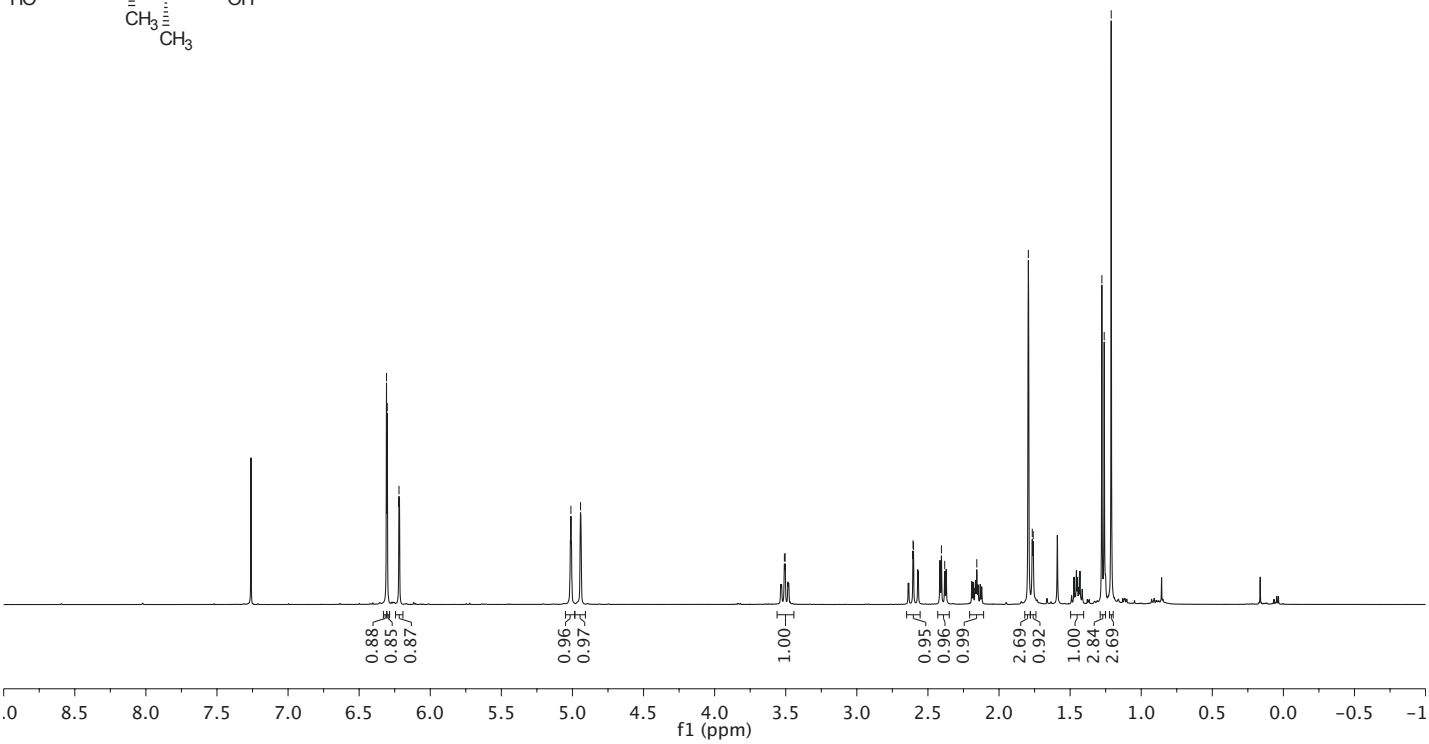


13C (CDCl3); 300.0 K; 100.62 MHZ

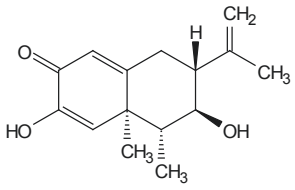


1H (CDCl3); 300.0 K; 400.13 MHZ

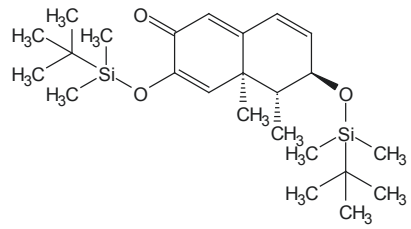




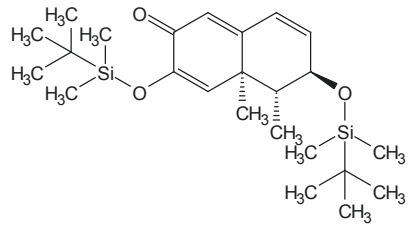
13C (CDCl3); 300.0 K; 100.62 MHZ



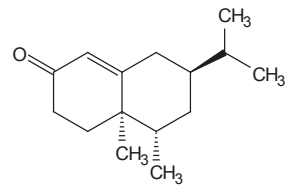
1H (CDCl3); 300.0 K; 400.23 MHZ



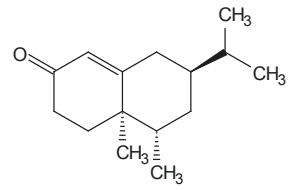
13C (CDCl3); 300.0 K; 100.65 MHZ



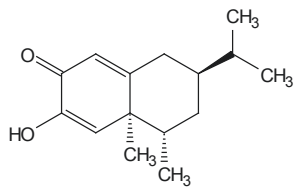
1H (CDCl3); 300.0 K; 400.13 MHZ



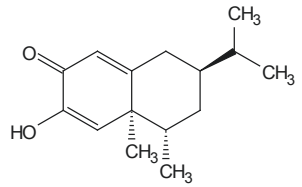
13C (CDCl3); 300.0 K; 100.62 MHZ



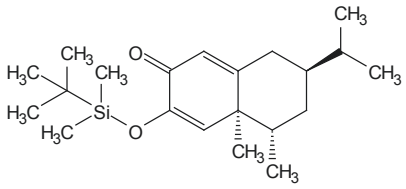
1H (CDCl3); 300.0 K; 400.13 MHZ



13C (CDCl3); 295.2 K; 100.62 MHZ



1H (CDCl3); 300.0 K; 400.13 MHZ

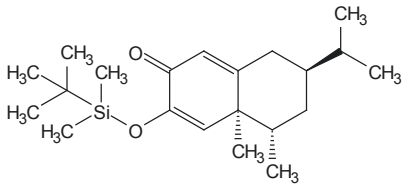


6.29 6.04 2.47 1.68 1.48 1.45 1.37 1.13 1.01 1.00 0.96 0.90 0.88 0.82 0.81 0.19 0.18

1.00 0.97 1.89 4.82 1.05 2.97 3.10 9.60 2.84 3.06 2.56 3.37

f1 (ppm)

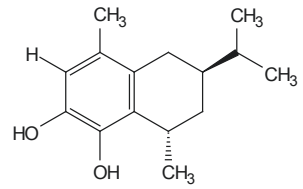
13C (CDCl3); 300.0 K; 100.62 MHZ



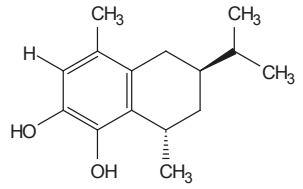
182.85 166.71 147.46 133.92 125.56 44.46 43.50 36.92 35.02 32.38 26.33 25.91 21.27 20.85 18.71 18.58 16.43 -4.33 -4.40

f1 (ppm)

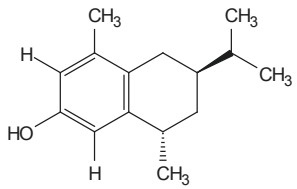
1H (CDCl3); 300.0 K; 500.13 MHZ

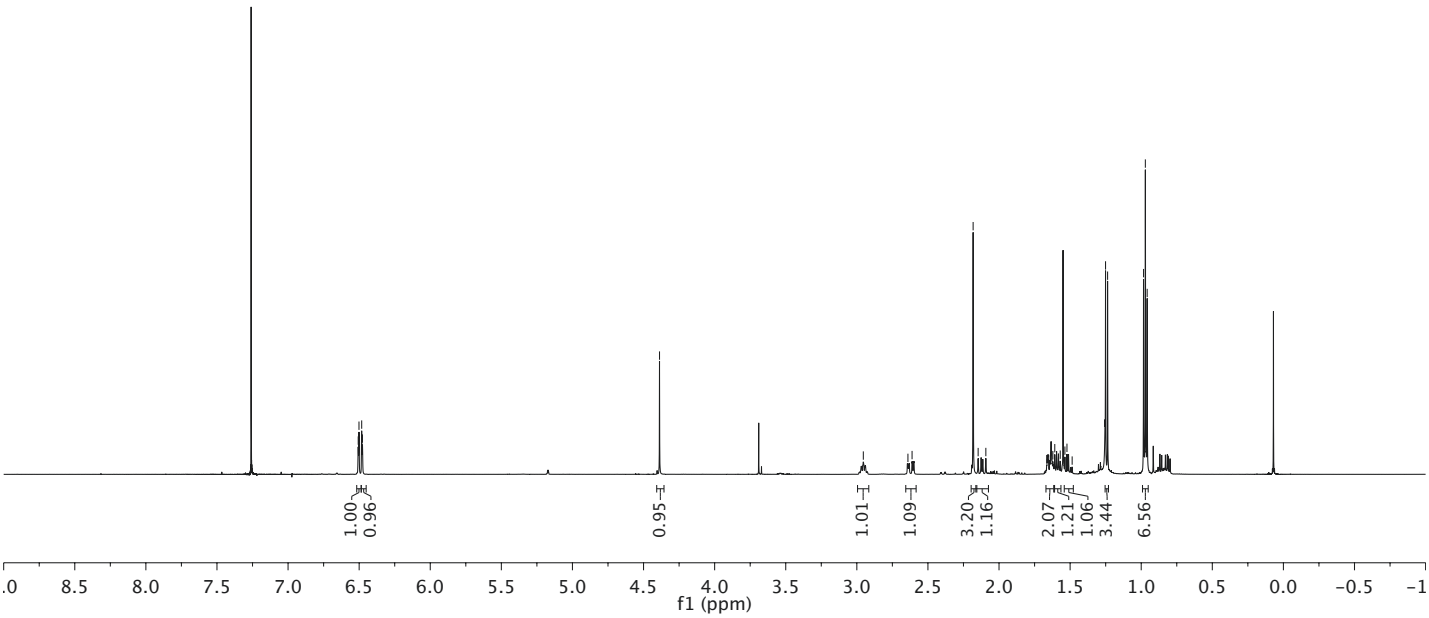


13C (CDCl3); 300.1 K; 125.77 MHZ

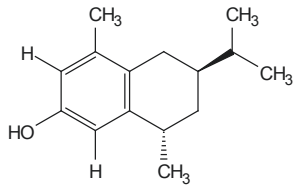


1H (CDCl3); 298.0 K; 500.13 MHZ

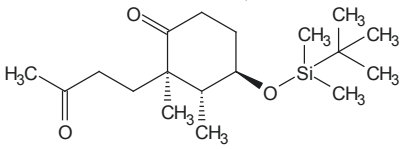




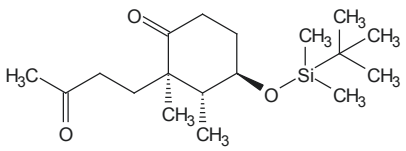
13C (CDCl3); 298.0 K; 125.77 MHZ



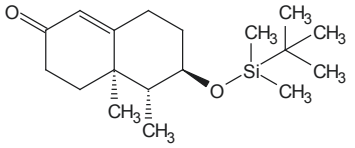
1H (CDCl3); 300.0 K; 400.13 MHZ



13C (CDCl3); 300.0 K; 100.62 MHZ



1H (CDCl3); 300.0 K; 400.13 MHZ

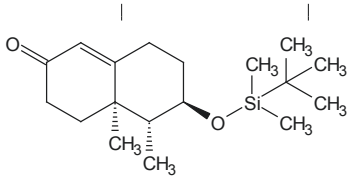


7.26 CHCl3
5.74
3.57
3.56
2.46
2.33
2.30
2.30
2.27
2.26
2.07
1.99
1.73
1.72
1.50
1.46
1.43
1.40
1.32
1.11
0.99
0.97
0.89
0.07
0.07

0.97
1.00
2.97
1.27
2.07
1.10
1.03
1.02
3.03
2.99
9.05
3.07
2.72

f1 (ppm)

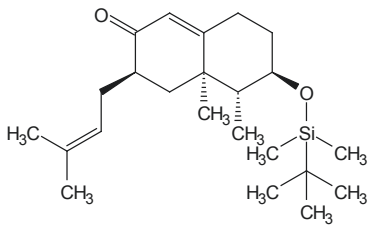
13C (CDCl3); 300.0 K; 100.62 MHZ



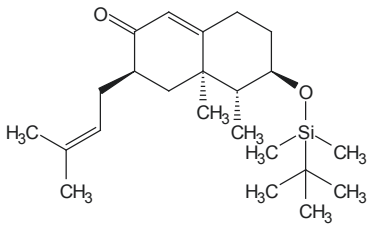
199.57
169.43
124.29
77.16 CDCl3
72.01
50.15
39.33
36.01
35.86
33.56
31.49
25.98
18.20
17.44
11.22
-3.86
-4.54

f1 (ppm)

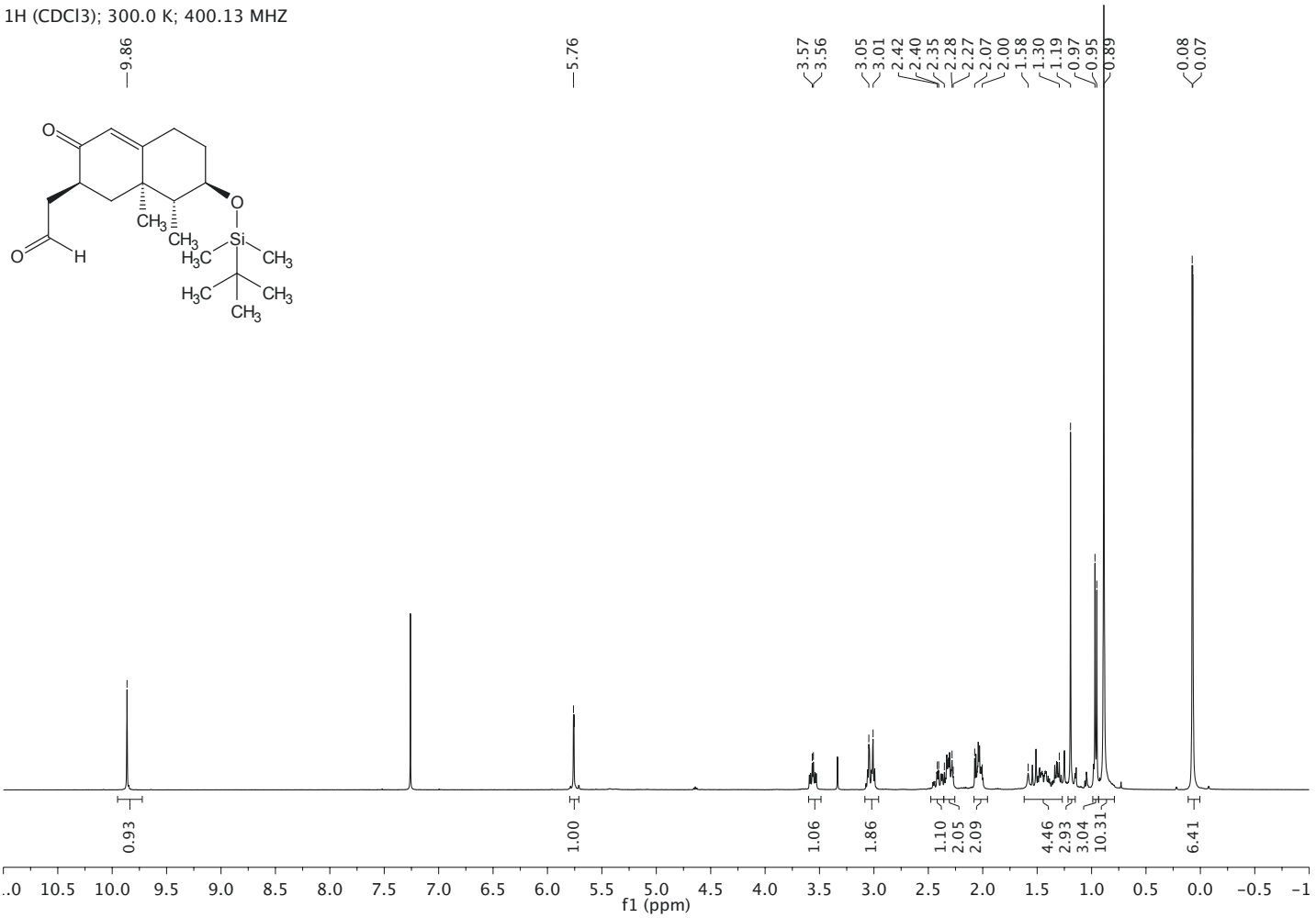
1H (CDCl3); 300.0 K; 400.13 MHZ



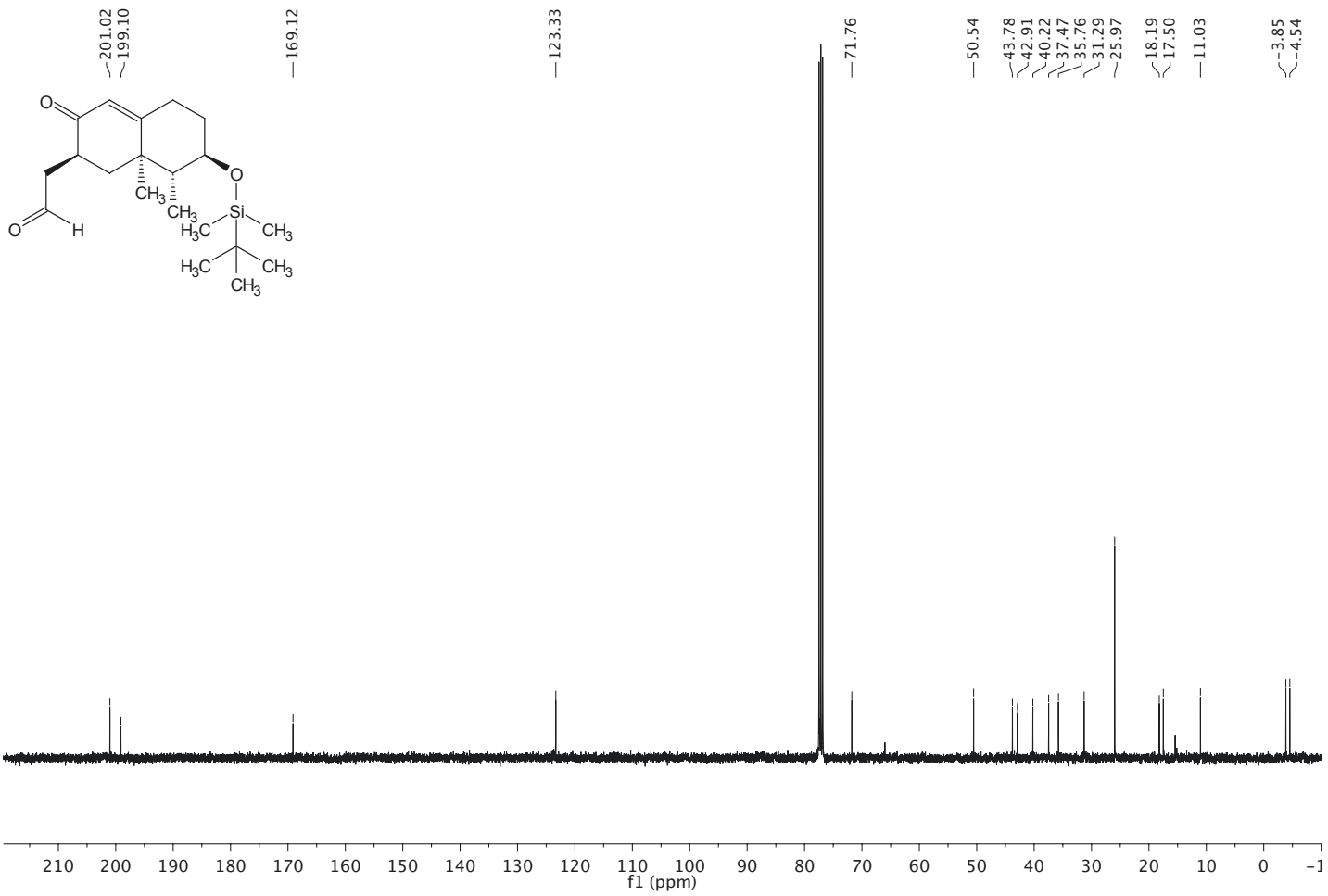
13C (CDCl3); 295.2 K; 100.62 MHZ



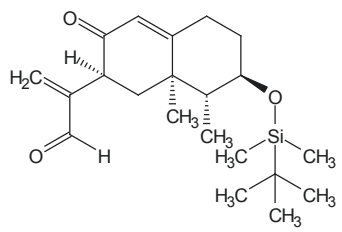
1H (CDCl3); 300.0 K; 400.13 MHZ



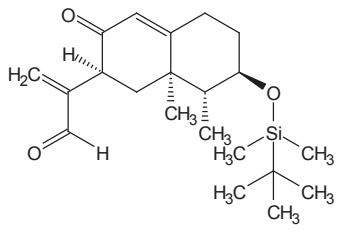
13C (CDCl3); 300.0 K; 100.62 MHZ



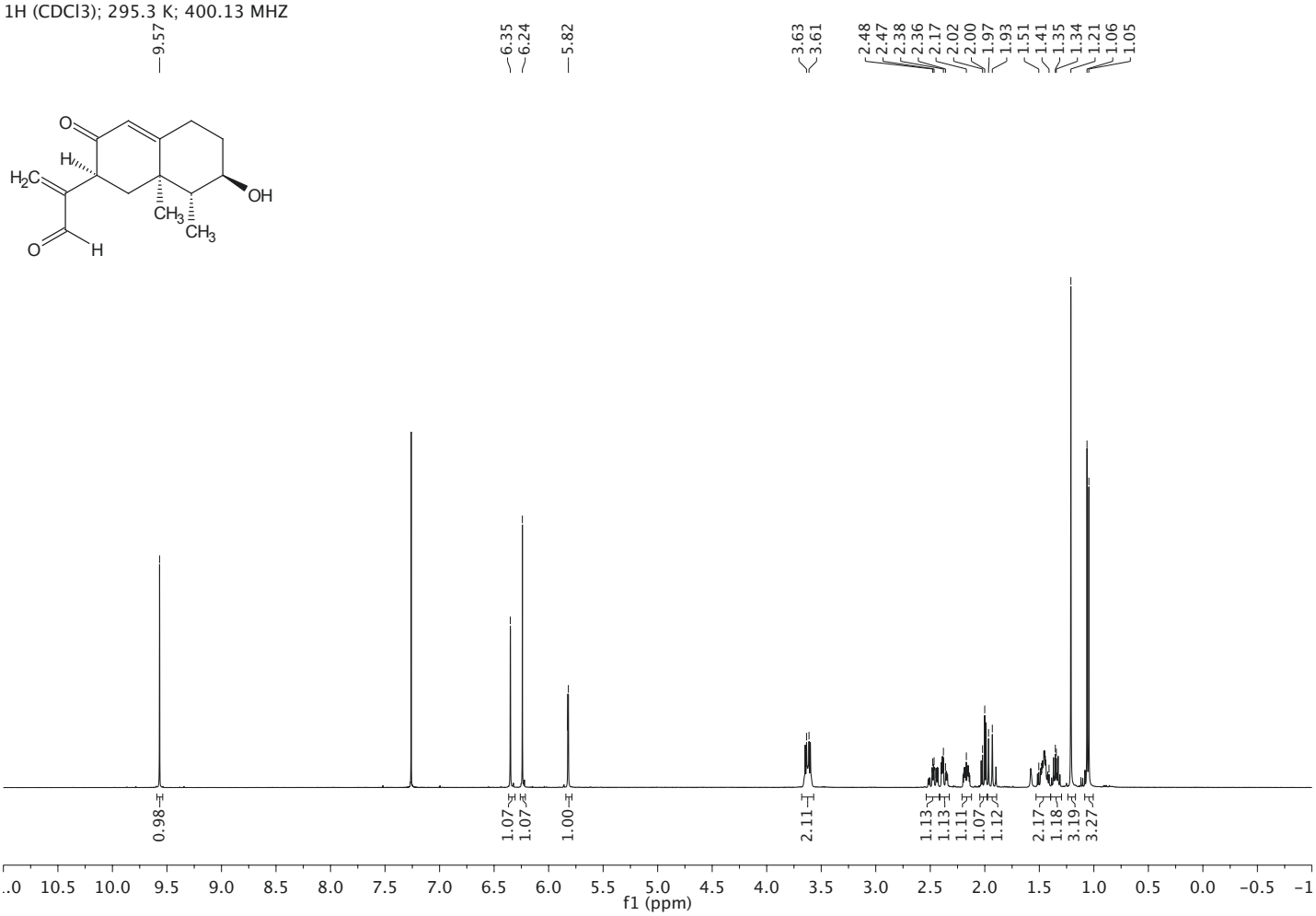
1H (CDCl3); 300.0 K; 400.13 MHZ



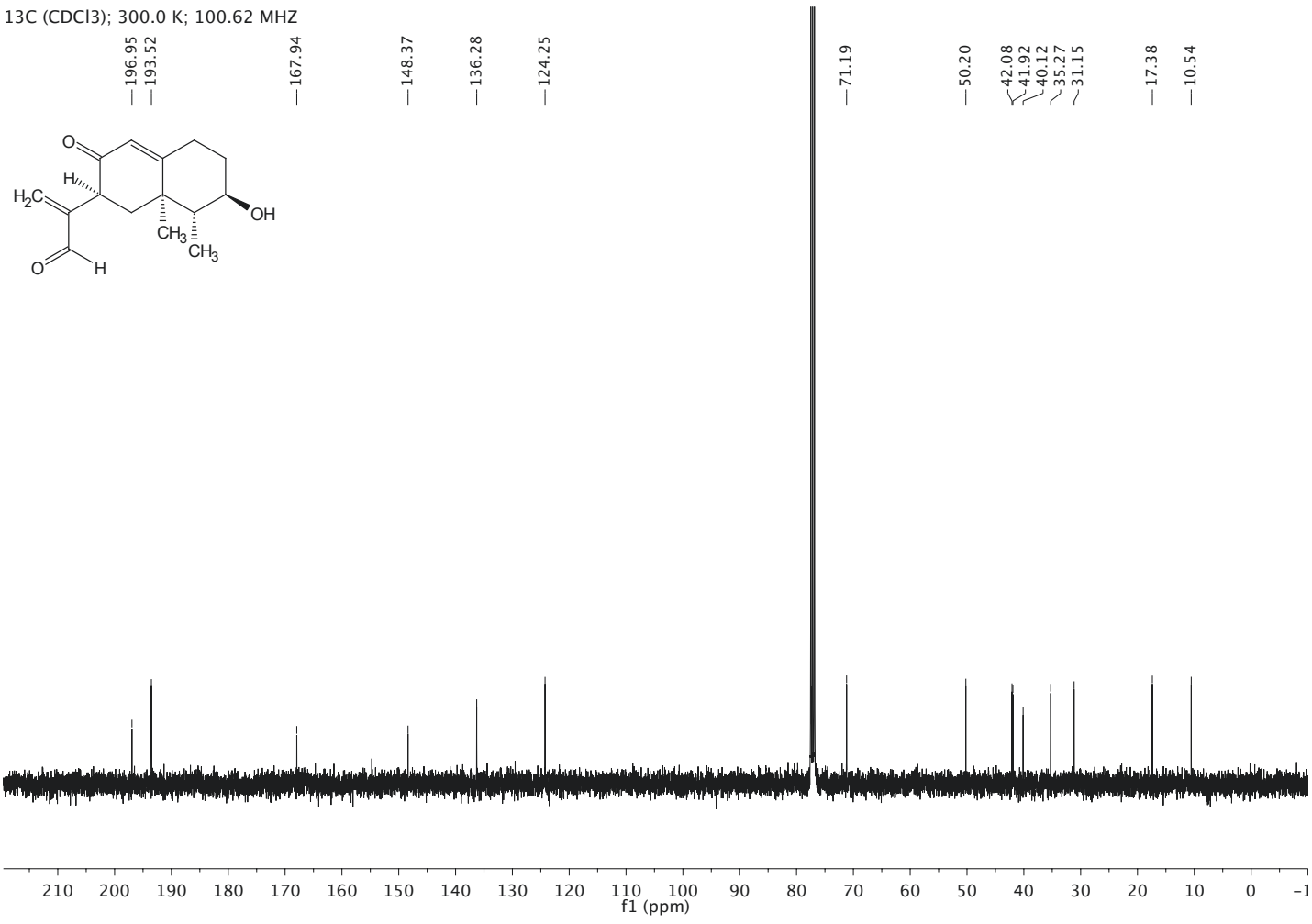
13C (CDCl3); 300.0 K; 100.62 MHZ



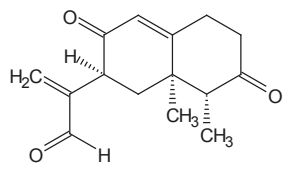
1H (CDCl3); 295.3 K; 400.13 MHZ



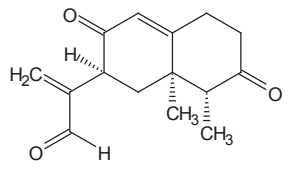
13C (CDCl3); 300.0 K; 100.62 MHZ



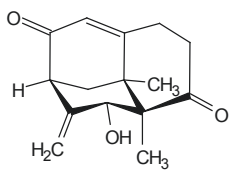
1H (CDCl3); 300.0 K; 400.13 MHZ



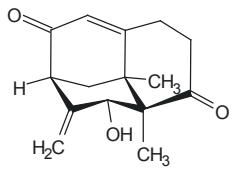
13C (CDCl3); 300.0 K; 100.62 MHZ



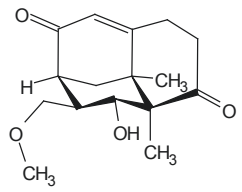
1H (CDCl3); 298.0 K; 500.25 MHZ



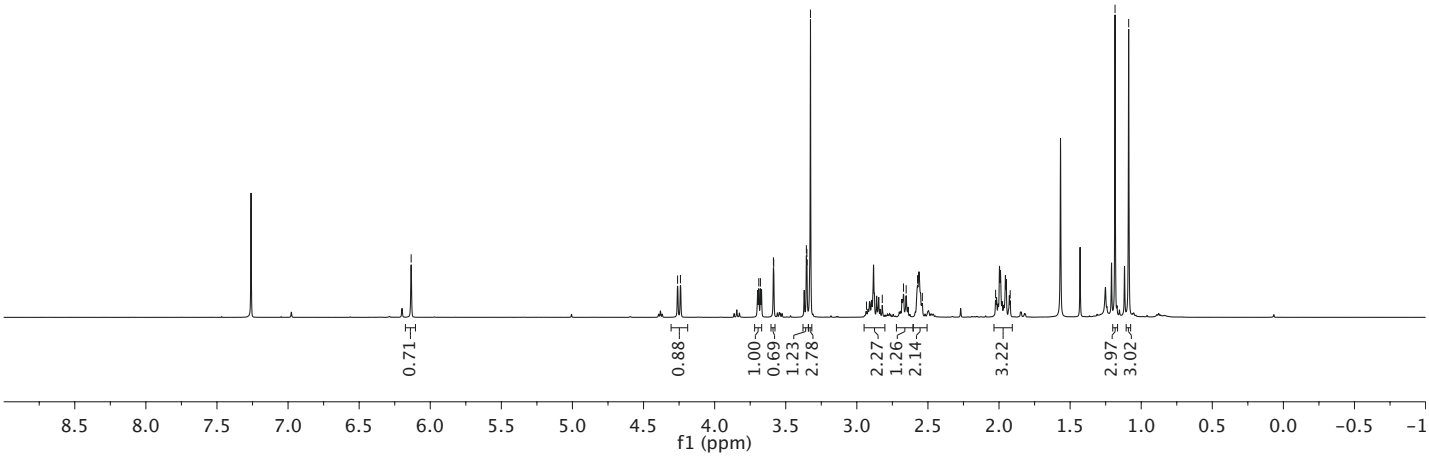
13C (CDCl3); 298.0 K; 125.80 MHZ



1H (CDCl3); 297.9 K; 500.13 MHZ

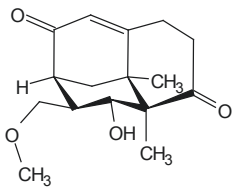


6.13
4.26
4.24
3.69
3.68
3.59
3.58
3.35
3.35
3.33
2.93
2.82
2.67
2.65
2.57
2.54
2.02
1.92
1.18
1.09

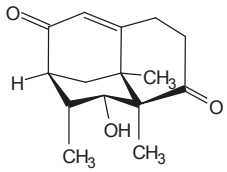


13C (CDCl3); 298.0 K; 125.77 MHZ

209.87
198.91
166.08
127.26
76.22
74.24
59.34
58.28
45.72
41.46
38.59
38.39
34.34
30.81
23.06
8.47



1H (CDCl3); 298.0 K; 500.30 MHZ



6.19

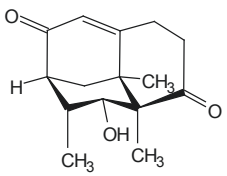
4.18
4.17

2.96
2.90
2.77
2.75
2.71
2.66
2.55
2.54
2.50
2.49
2.20
2.07
2.05
1.83
1.81

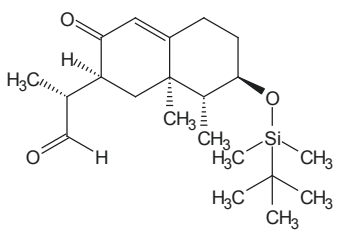
1.18
1.14
1.13
1.11

13C (CDCl3); 298.0 K; 125.81 MHZ

211.61
200.86
165.52
127.64
69.44
58.25
49.06
41.09
38.96
34.61
30.33
29.44
23.67
13.97
11.03

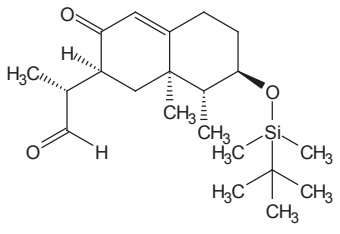


1H (CDCl3); 298.0 K; 500.25 MHZ



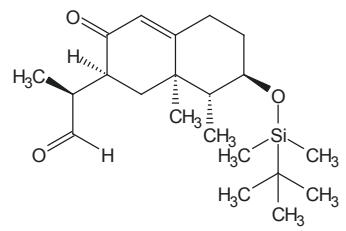
f1 (ppm)

13C (CDCl3); 298.0 K; 125.80 MHZ

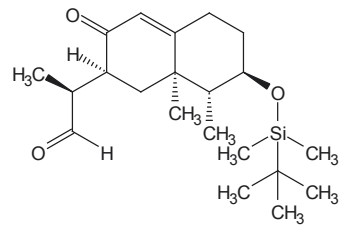


f1 (ppm)

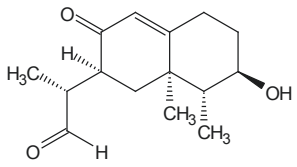
1H (CDCl3); 298.0 K; 500.25 MHZ



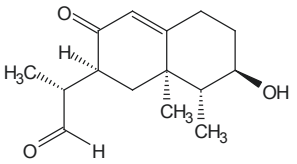
13C (CDCl3); 298.0 K; 125.80 MHZ



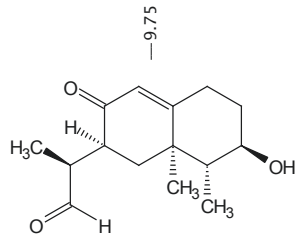
1H (CDCl3); 298.0 K; 500.13 MHZ



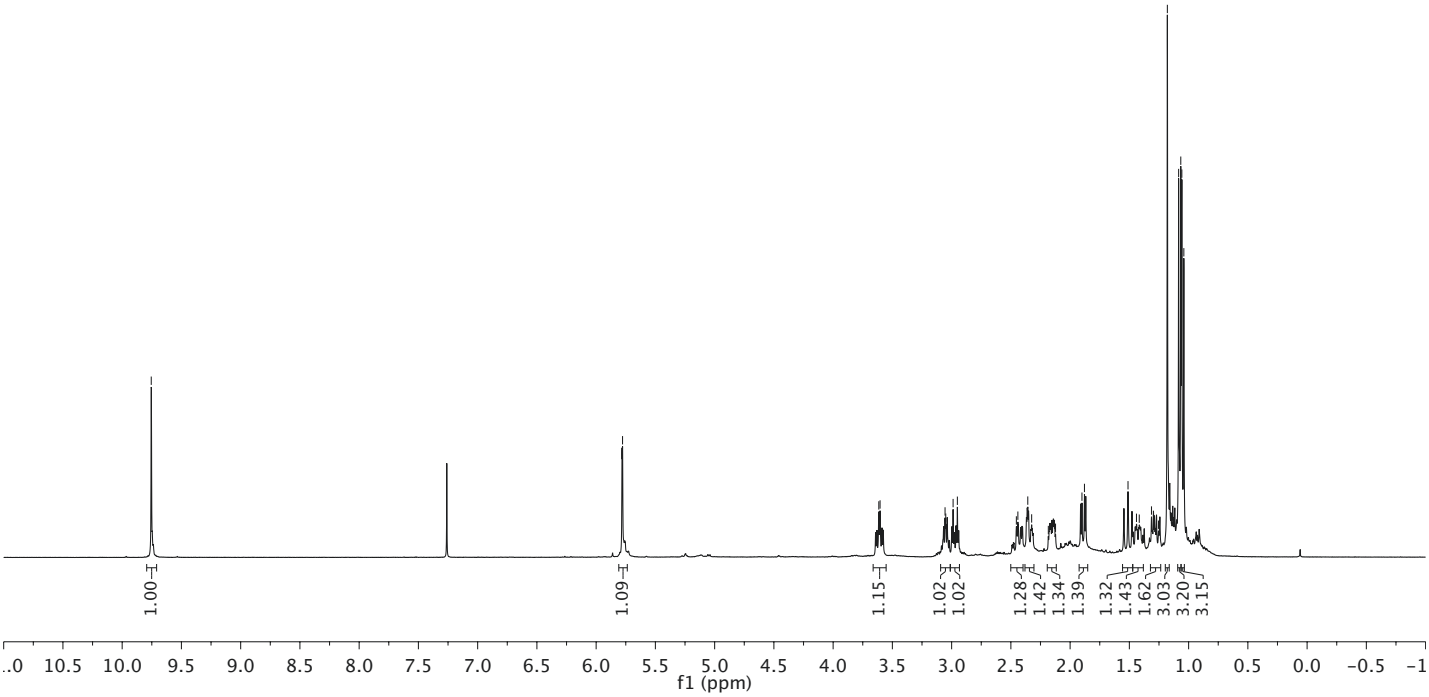
13C (CDCl3); 298.1 K; 125.77 MHZ



1H (CDCl3); 298.0 K; 400.23 MHZ



9.75 5.78 3.61 3.60 3.06 3.05 2.99 2.95 2.45 2.44 2.36 2.32 2.18 2.12 1.90 1.88 1.51 1.44 1.42 1.31 1.25 1.18 1.08 1.07 1.06 1.04



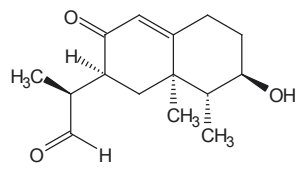
1.00 1.09 1.15 1.02 1.02 1.28 1.42 1.34 1.39 1.32 1.43 1.62 3.03 3.20 3.15

..0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

f1 (ppm)

13C (CDCl3); 298.1 K; 100.65 MHZ

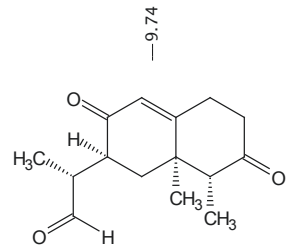
204.24 198.60 168.53 124.02 71.09 50.40 44.86 42.01 40.01 38.25 35.22 31.13 17.34 10.52 10.19



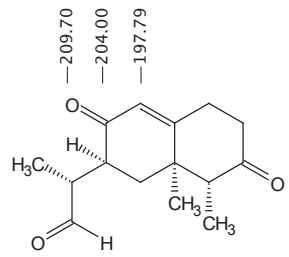
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1

f1 (ppm)

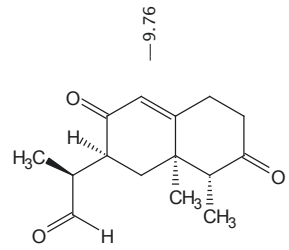
1H (CDCl3); 298.0 K; 500.13 MHZ



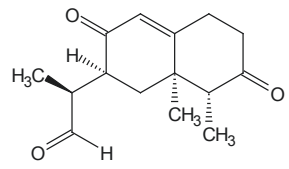
13C (CDCl3); 298.0 K; 125.77 MHZ



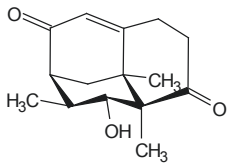
1H (CDCl3); 298.1 K; 400.13 MHZ

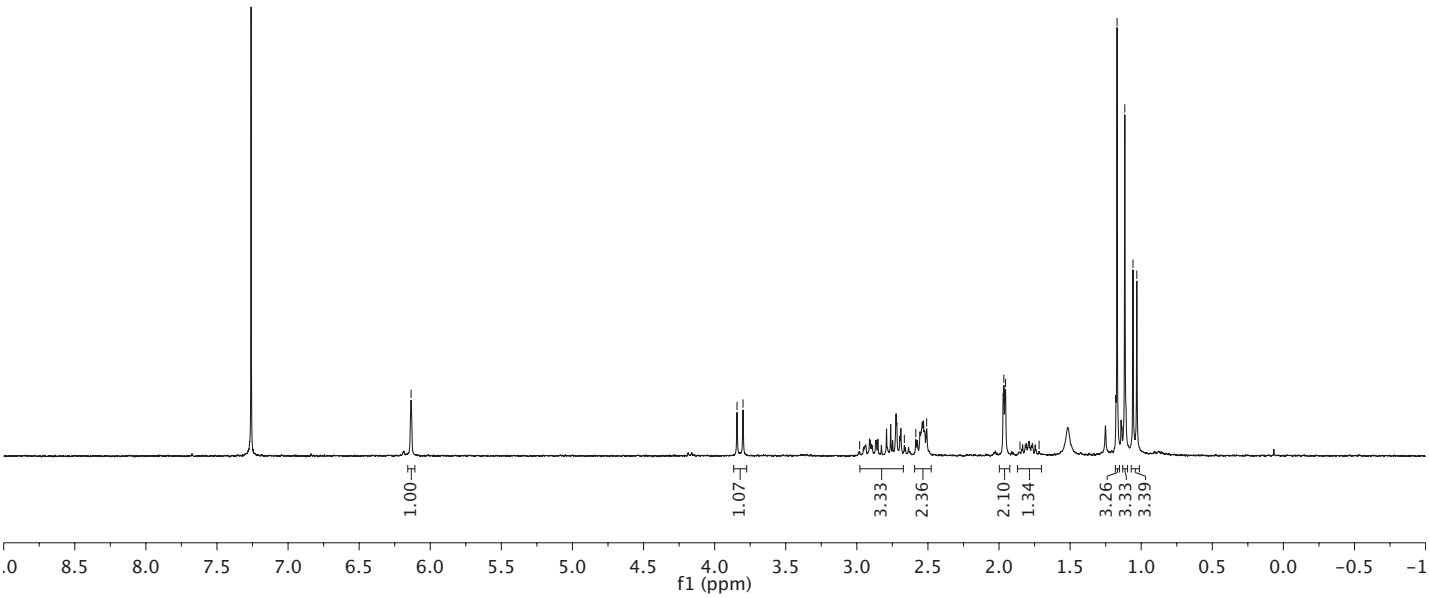


13C (CDCl3); 298.0 K; 100.65 MHZ

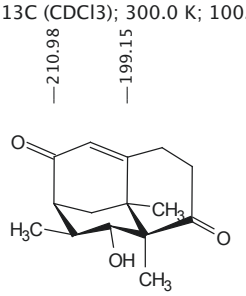


1H (CDCl3); 297.0 K; 250.13 MHZ

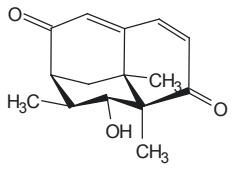




13C (CDCl3); 300.0 K; 100.62 MHZ



1H (CDCl3); 298.6 K; 400.13 MHZ

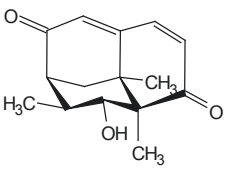


7.30
7.28
6.10
6.05
6.03
3.53
3.50
2.53
2.51
2.13
2.11
1.91
1.88
1.70
1.25
1.22
1.03
1.02

1.07
0.99
1.00
1.07
1.07
1.15
2.27
0.93
3.17
3.08
3.19

f1 (ppm)

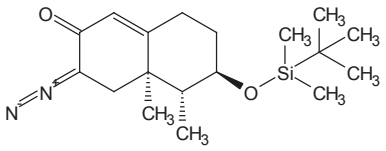
13C (CDCl3); 300.0 K; 100.62 MHZ



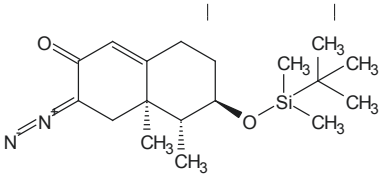
201.14
198.48
160.45
143.48
129.52
126.11
72.89
55.77
48.86
42.87
37.14
33.22
24.62
16.55
7.96

f1 (ppm)

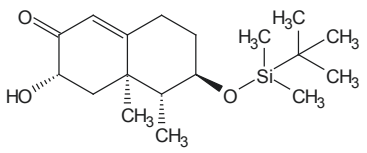
1H (CDCl3); 300.0 K; 400.13 MHZ



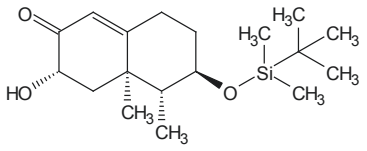
13C (CDCl3); 300.0 K; 100.62 MHZ



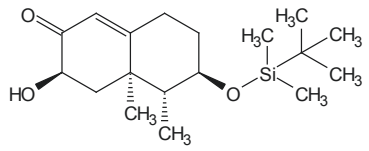
1H (CDCl3); 300.0 K; 500.13 MHZ



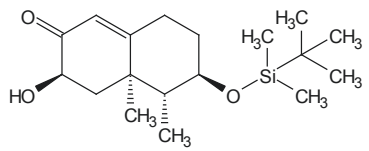
13C (CDCl3); 300.0 K; 100.62 MHZ



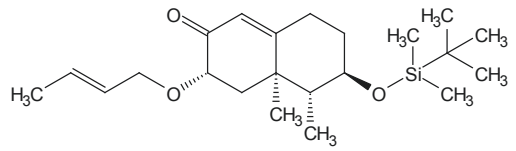
1H (CDCl3); 300.0 K; 500.13 MHZ



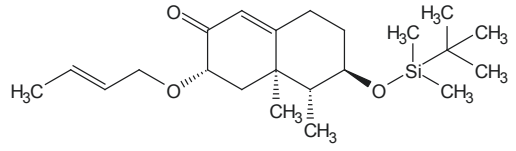
13C (CDCl3); 300.0 K; 125.77 MHZ



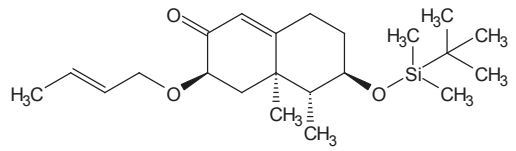
1H (CDCl3); 298.0 K; 500.13 MHZ



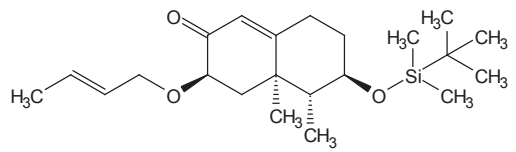
13C (CDCl3); 300.0 K; 100.62 MHZ



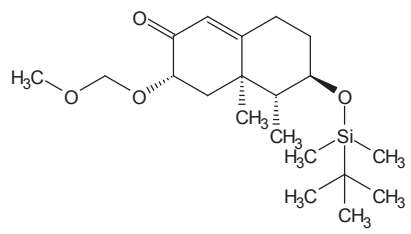
1H (CDCl3); 298.0 K; 500.13 MHZ



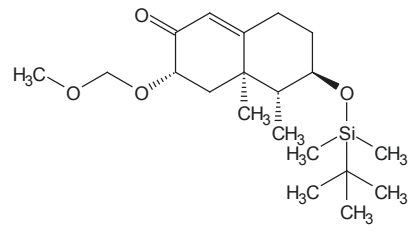
13C (CDCl3); 300.0 K; 100.62 MHZ



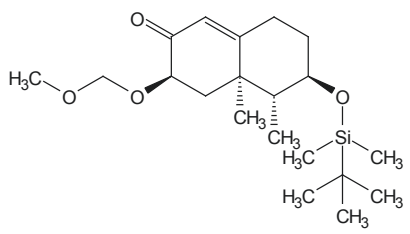
1H (CDCl3); 300.0 K; 400.13 MHZ



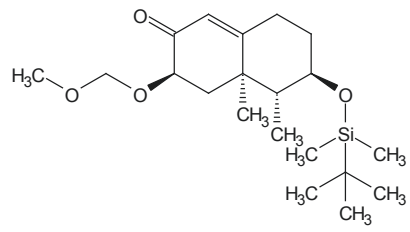
13C (CDCl3); 300.0 K; 100.62 MHZ



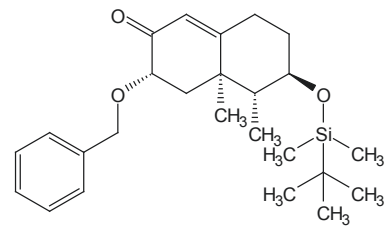
1H (CDCl3); 300.0 K; 400.13 MHZ



13C (CDCl3); 300.0 K; 100.62 MHZ



1H (CDCl3); 300.0 K; 400.23 MHZ

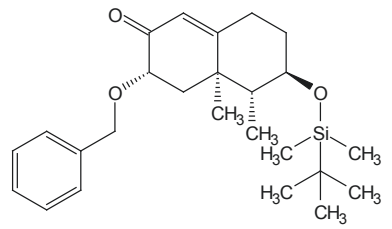


7.36 7.27 5.77 4.80 4.77 4.56 4.53 3.86 3.85 3.61 3.60 2.49 2.48 2.26 2.25 2.13 2.06 1.98 1.96 1.55 1.21 1.01 0.99 0.89 0.07 0.07

4.79 1.00 1.03 1.04 1.05 1.05 1.11 1.07 2.09 1.10 1.27 3.19 3.14 9.17 6.26 3.12

f1 (ppm)

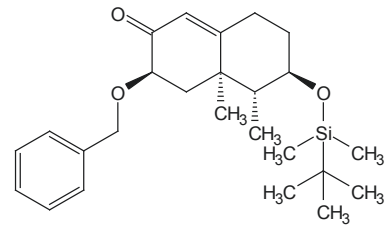
13C (CDCl3); 297.9 K; 100.62 MHZ



197.16 170.29 138.39 128.47 127.69 127.67 121.81 76.11 72.21 72.01 49.13 40.95 40.19 37.06 31.50 25.98 21.70 18.19 11.82 -3.85 -4.54

f1 (ppm)

1H (CDCl3); 297.6 K; 400.13 MHZ

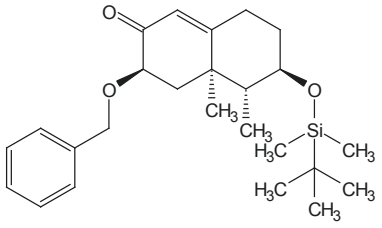


7.43 7.40 7.37 7.33 7.30 7.27 5.71 5.71 5.04 5.02 4.67 4.64 4.05 4.03 3.54 3.53 2.41 2.30 2.25 2.23 2.02 1.77 1.45 1.44 1.37 1.36 1.13 0.97 0.96 0.89 0.07 0.06

1.99 2.19 0.96 1.00 1.04 1.00 1.06 1.09 2.16 1.10 1.15 1.09 1.34 1.17 3.10 3.11 9.40 2.91 3.36

f1 (ppm)

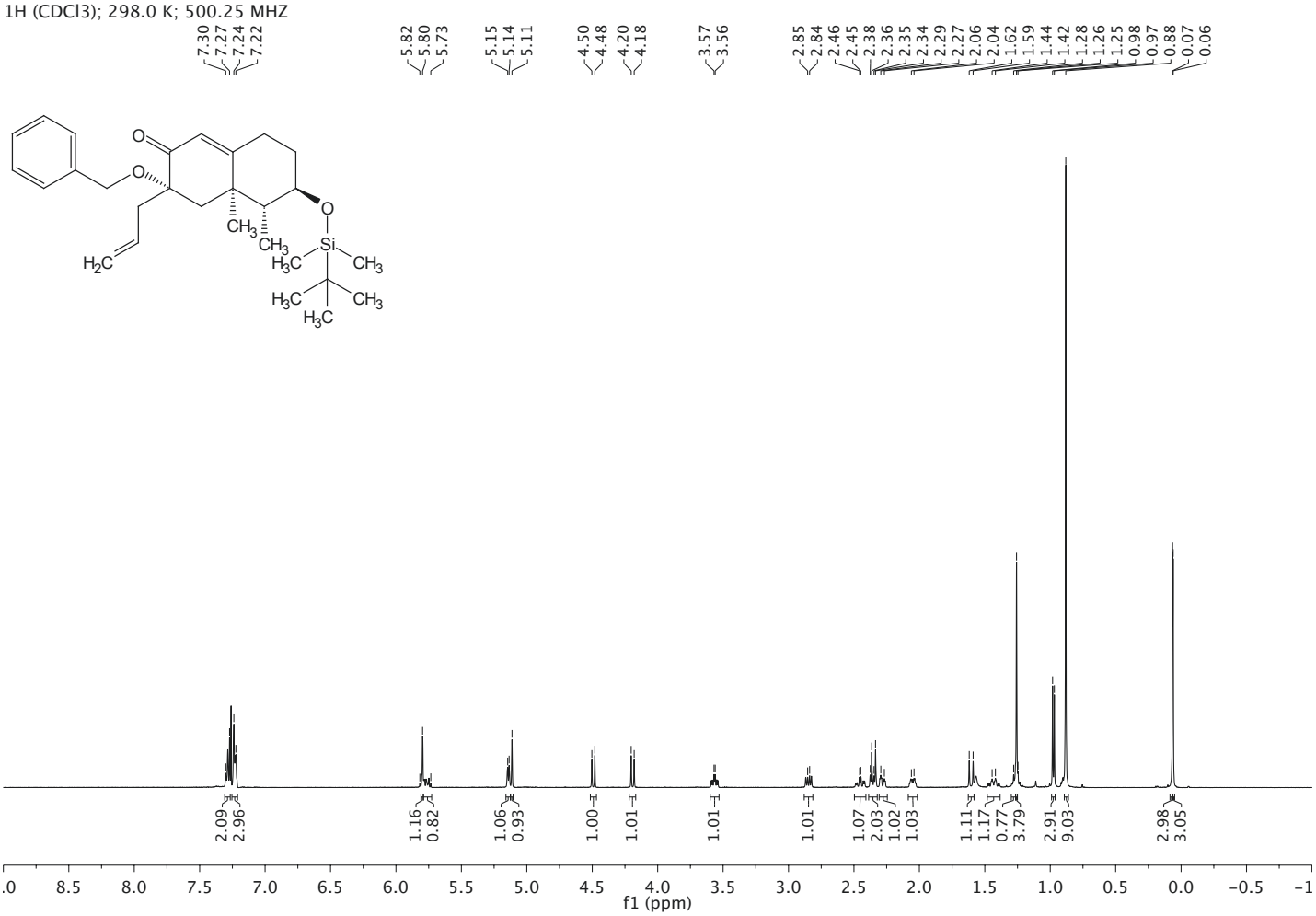
13C (CDCl3); 297.8 K; 100.62 MHZ



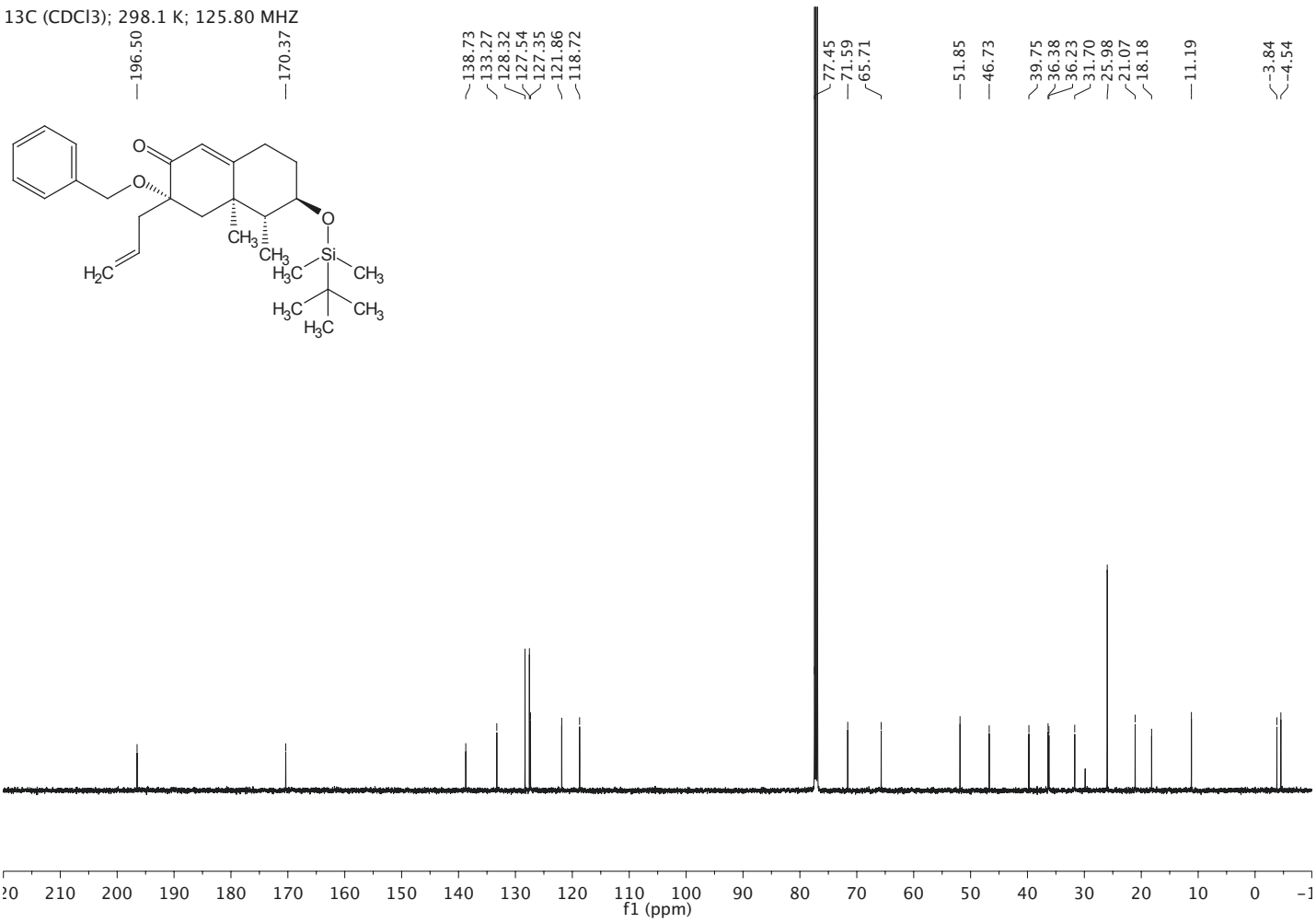
198.80 168.27 138.35 128.55 128.05 127.85 122.85 75.42 72.90 71.48 50.69 43.20 41.39 35.86 31.05 25.97 18.19 18.09 10.97 -3.87 -4.55

f1 (ppm)

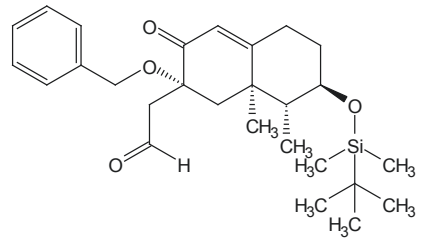
1H (CDCl3); 298.0 K; 500.25 MHZ



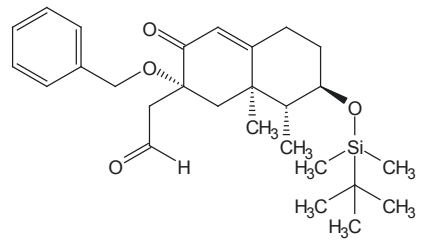
13C (CDCl3); 298.1 K; 125.80 MHZ



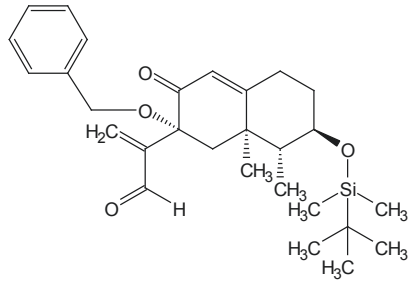
1H (CDCl3); 298.0 K; 500.25 MHZ



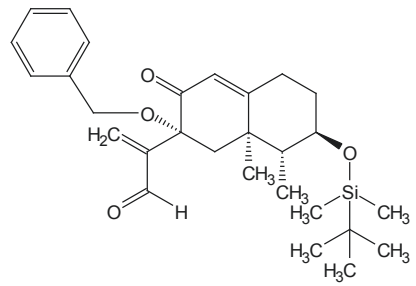
13C (CDCl3); 298.1 K; 125.80 MHZ



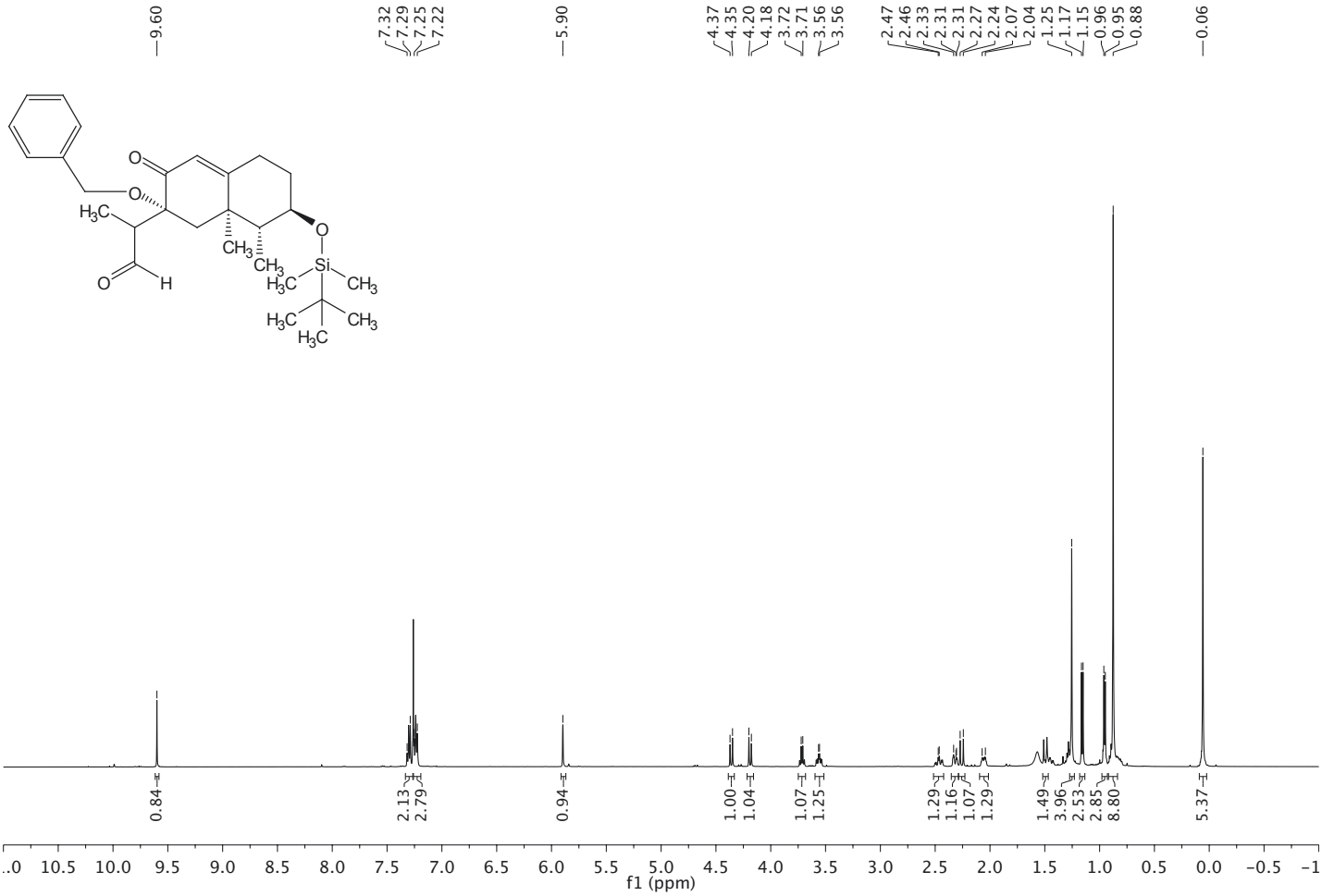
1H (CDCl3); 298.0 K; 500.25 MHZ



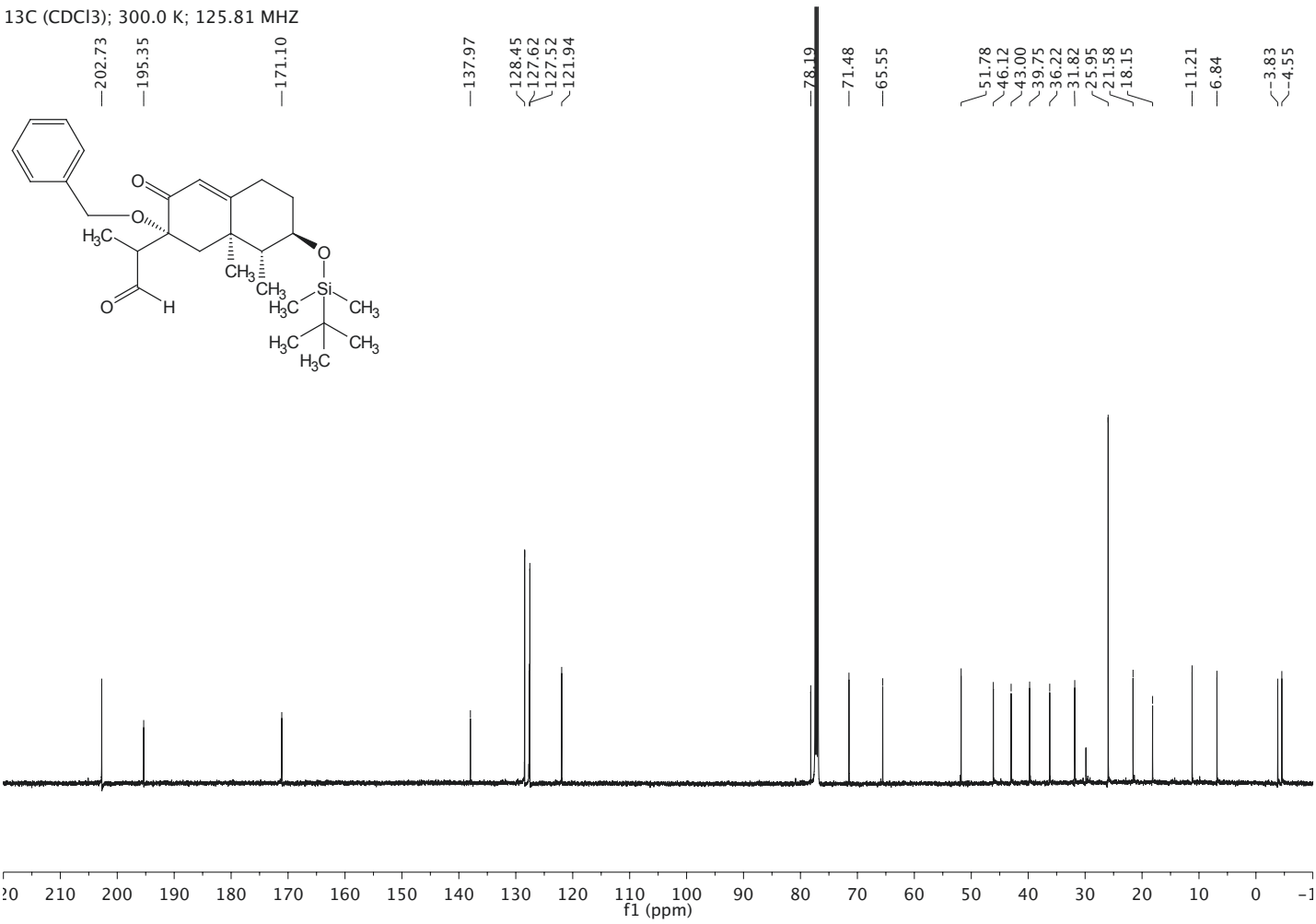
13C (CDCl3); 298.1 K; 125.80 MHZ



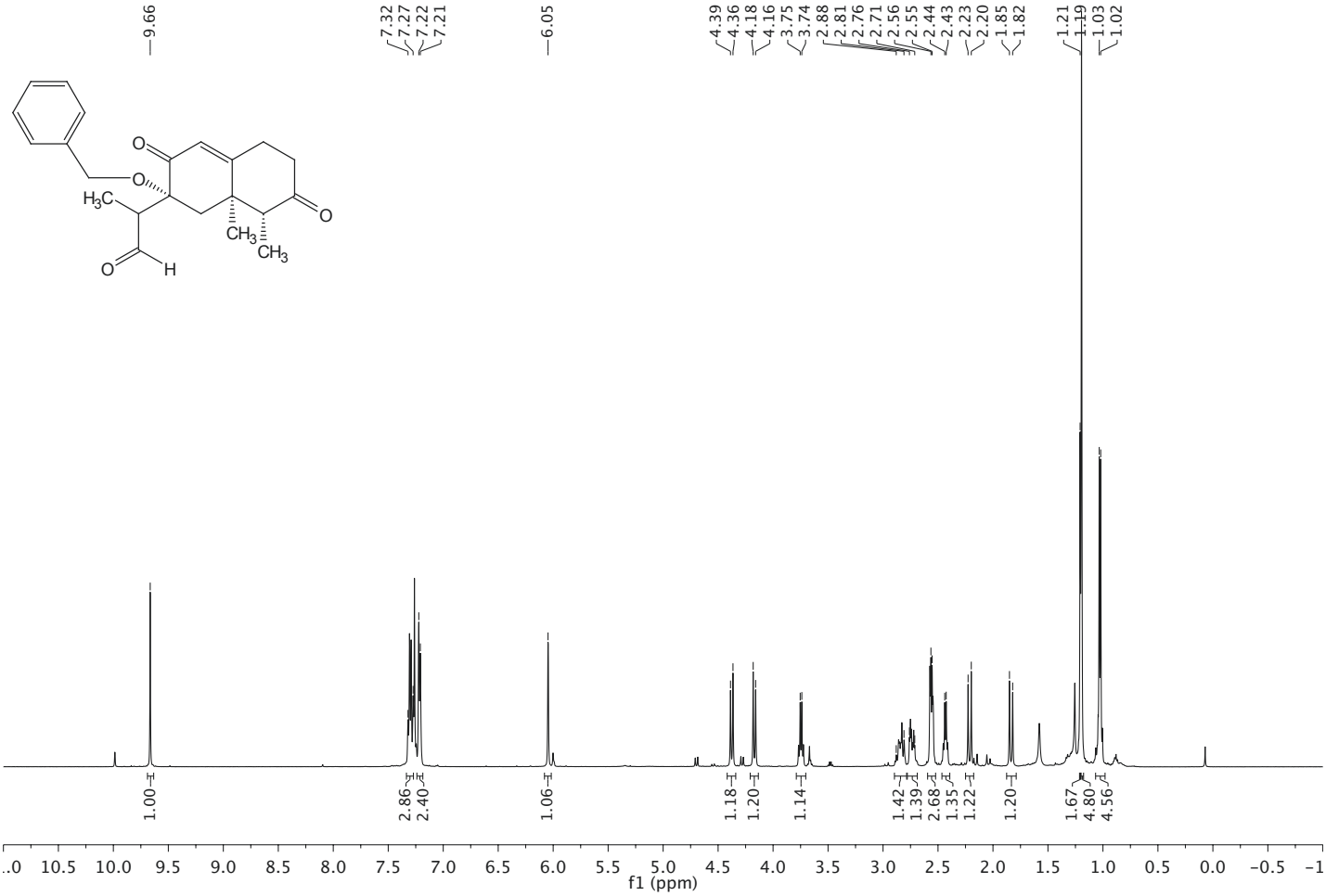
1H (CDCl3); 300.0 K; 500.30 MHZ



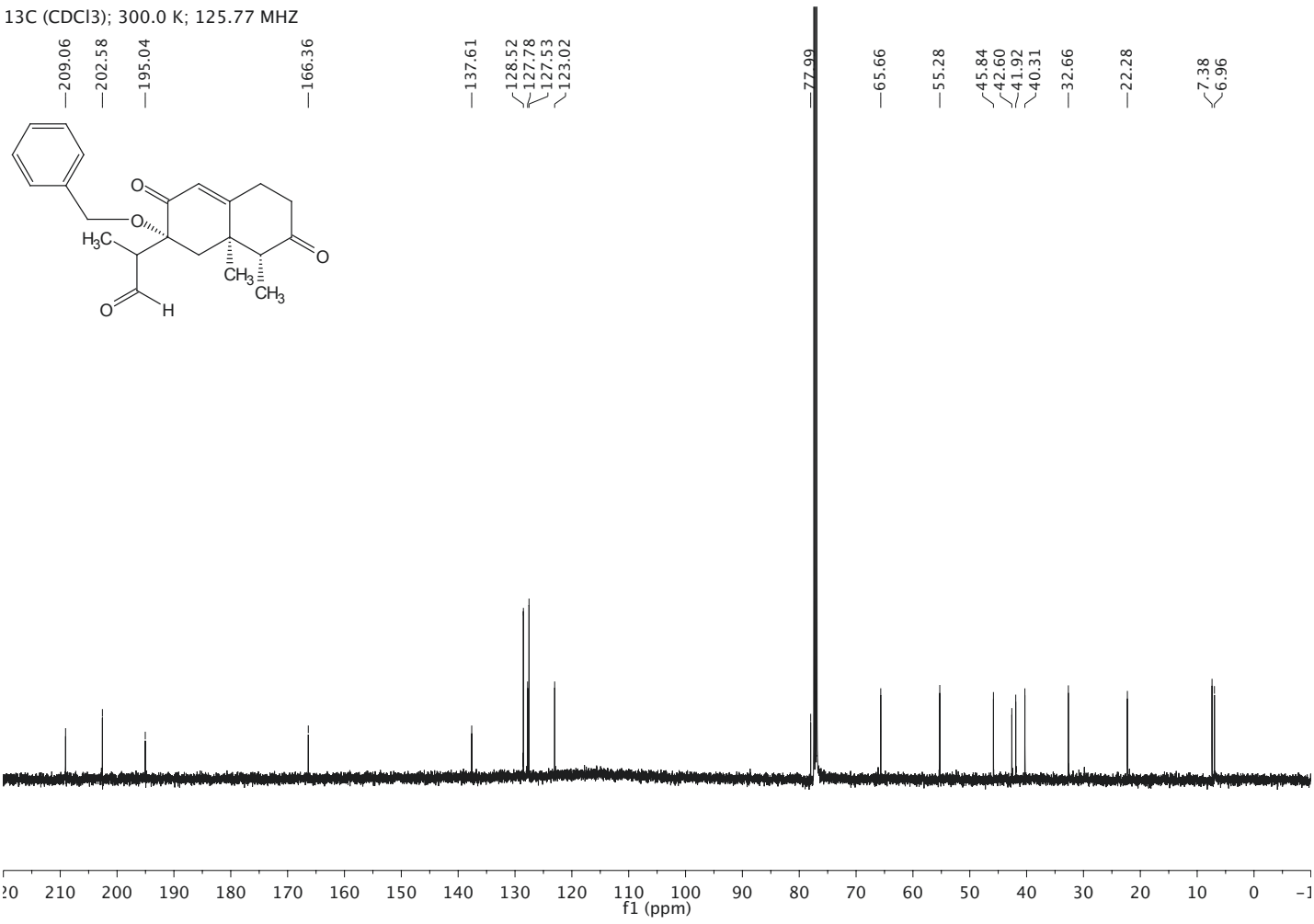
13C (CDCl3); 300.0 K; 125.81 MHZ



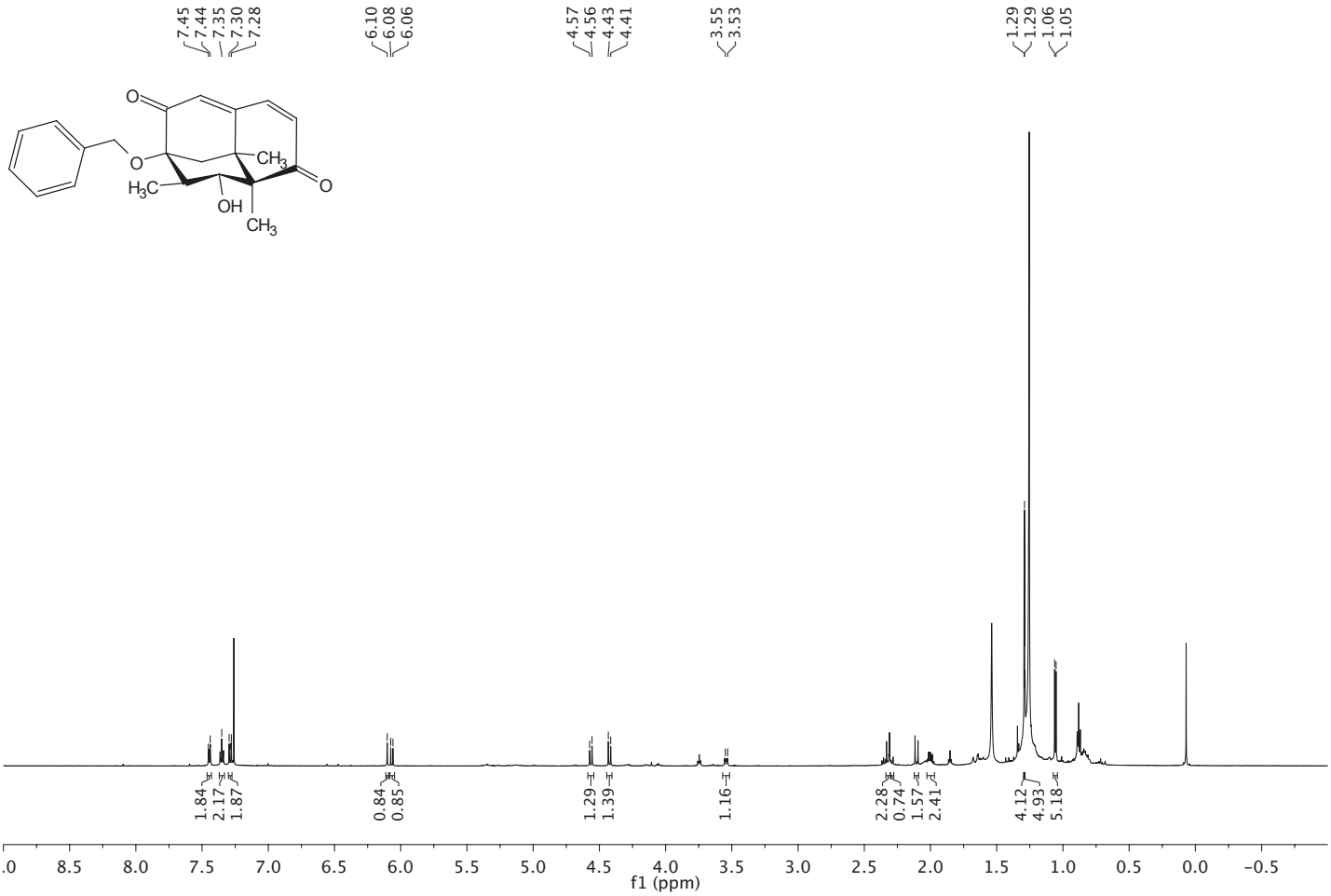
1H (CDCl3); 300.0 K; 500.13 MHZ



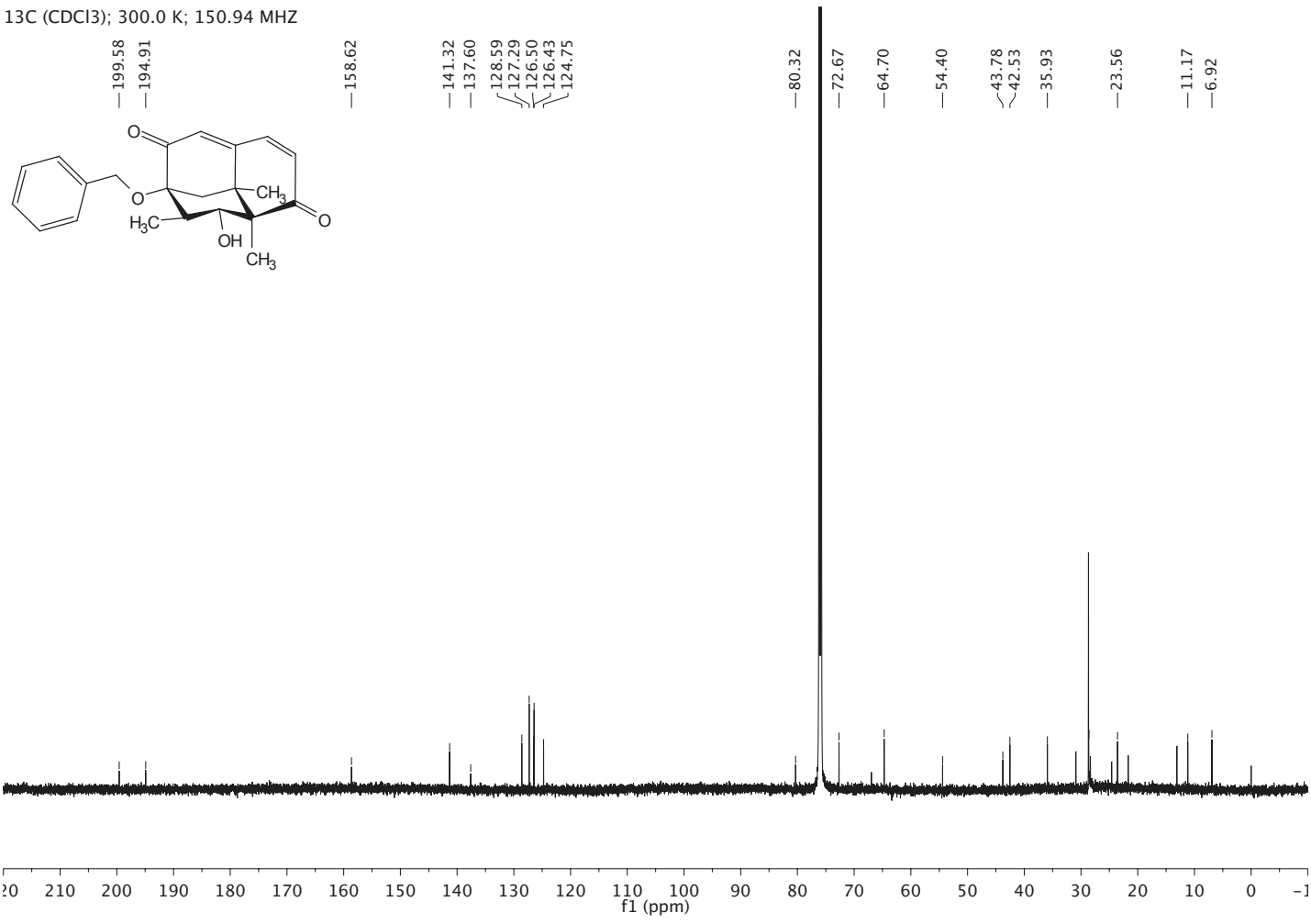
13C (CDCl3); 300.0 K; 125.77 MHZ



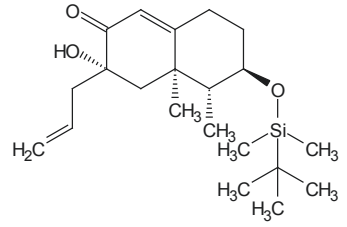
1H (CDCl3); 300.0 K; 600.23 MHZ



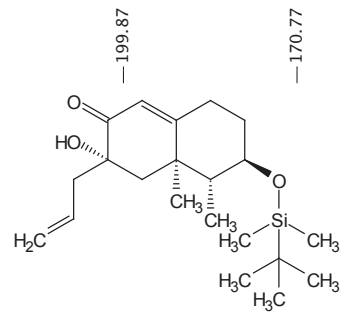
13C (CDCl3); 300.0 K; 150.94 MHZ



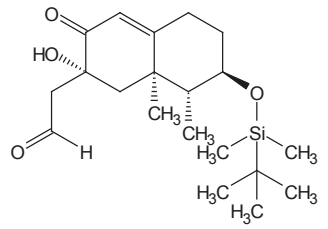
1H (CDCl3); 300.0 K; 500.13 MHZ



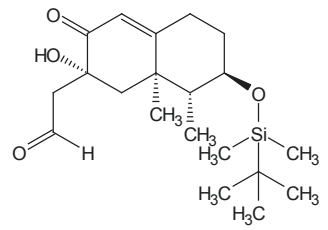
13C (CDCl3); 300.1 K; 125.77 MHZ



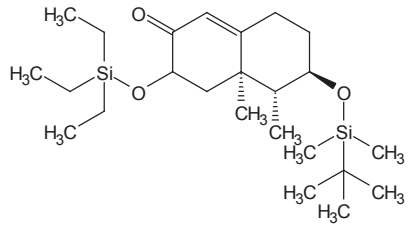
1H (CDCl3); 298.0 K; 500.13 MHZ



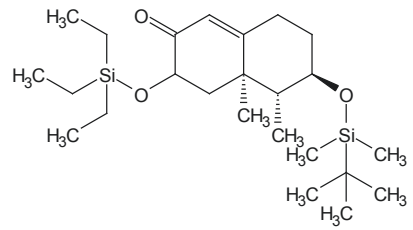
13C (CDCl3); 298.1 K; 125.77 MHZ



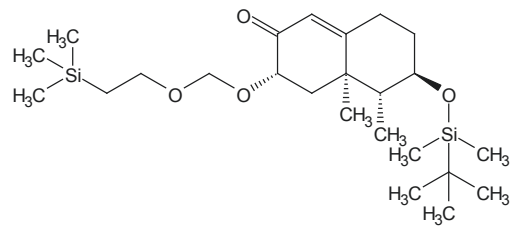
1H (CDCl3); 300.0 K; 500.30 MHZ



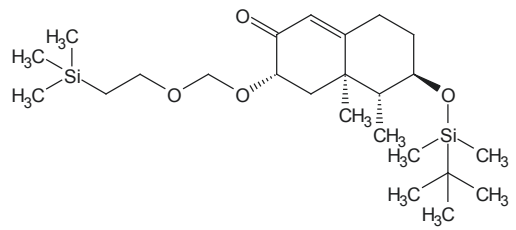
13C (CDCl3); 300.0 K; 125.81 MHZ



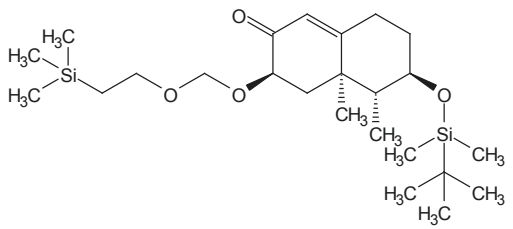
1H (CDCl3); 298.0 K; 500.25 MHZ



13C (CDCl3); 298.1 K; 125.80 MHZ



1H (CDCl3); 300.0 K; 400.13 MHZ



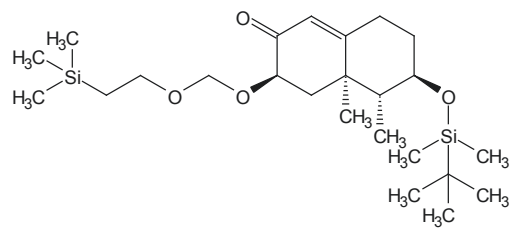
5.72 5.71 4.92 4.90 4.88 4.86 4.31 4.29 3.78 3.63 3.57 3.55 2.38 2.36 2.28 2.26 2.06 2.00 1.74 1.46 1.45 1.38 1.38 1.21 1.00 0.98 0.96 0.91 0.89 0.08 0.07 0.03

1.00 0.98 0.97 0.99 2.40 1.12 2.07 1.41 1.19 1.15 1.41 1.10 2.92 3.35 2.34 9.16 3.60 3.31 9.28

.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

f1 (ppm)

13C (CDCl3); 300.0 K; 100.62 MHZ



197.89 168.44 122.77 94.74 73.02 71.50 65.59 50.68 43.37 41.34 35.85 31.12 25.98 18.34 18.24 18.20 10.97 -1.23 -3.85 -4.54

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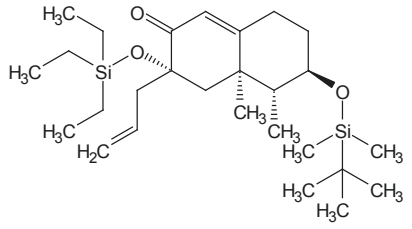
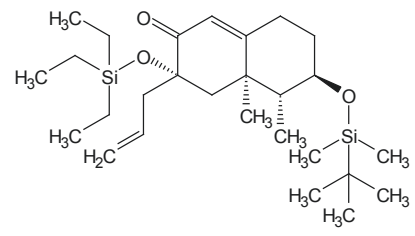
f1 (ppm)

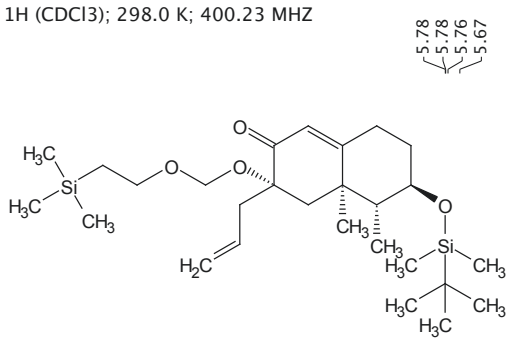
1H (CDCl3); 298.0 K; 500.30 MHZ



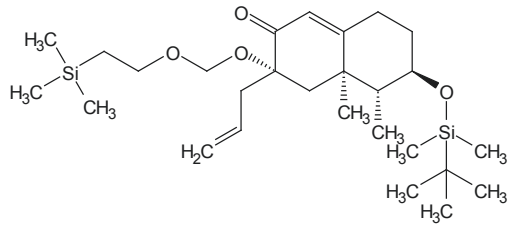
13C (CDCl3); 298.0 K; 125.81 MHZ



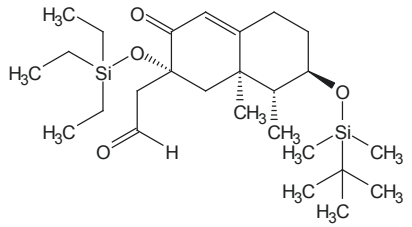
1H (CDCl3); 298.0 K; 400.23 MHZ



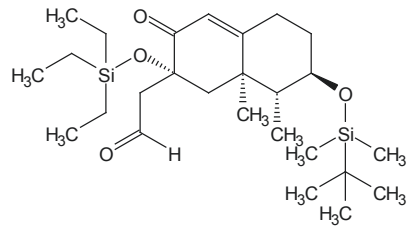
13C (CDCl3); 298.0 K; 100.65 MHZ



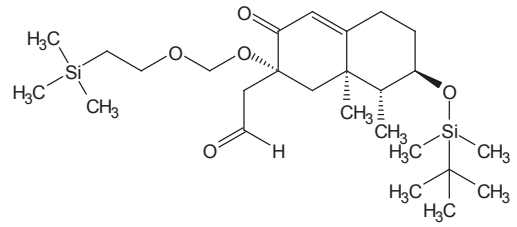
1H (CDCl3); 298.0 K; 400.23 MHZ



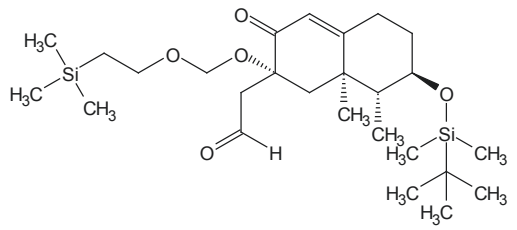
13C (CDCl3); 298.1 K; 125.77 MHZ



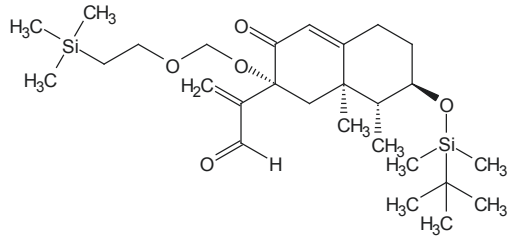
1H (CDCl3); 298.0 K; 400.23 MHZ



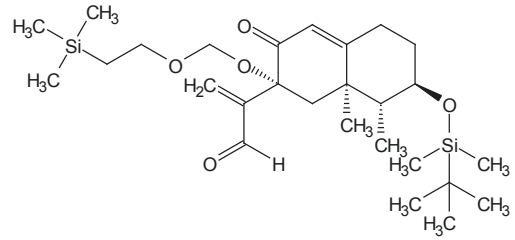
13C (CDCl3); 298.0 K; 100.65 MHZ



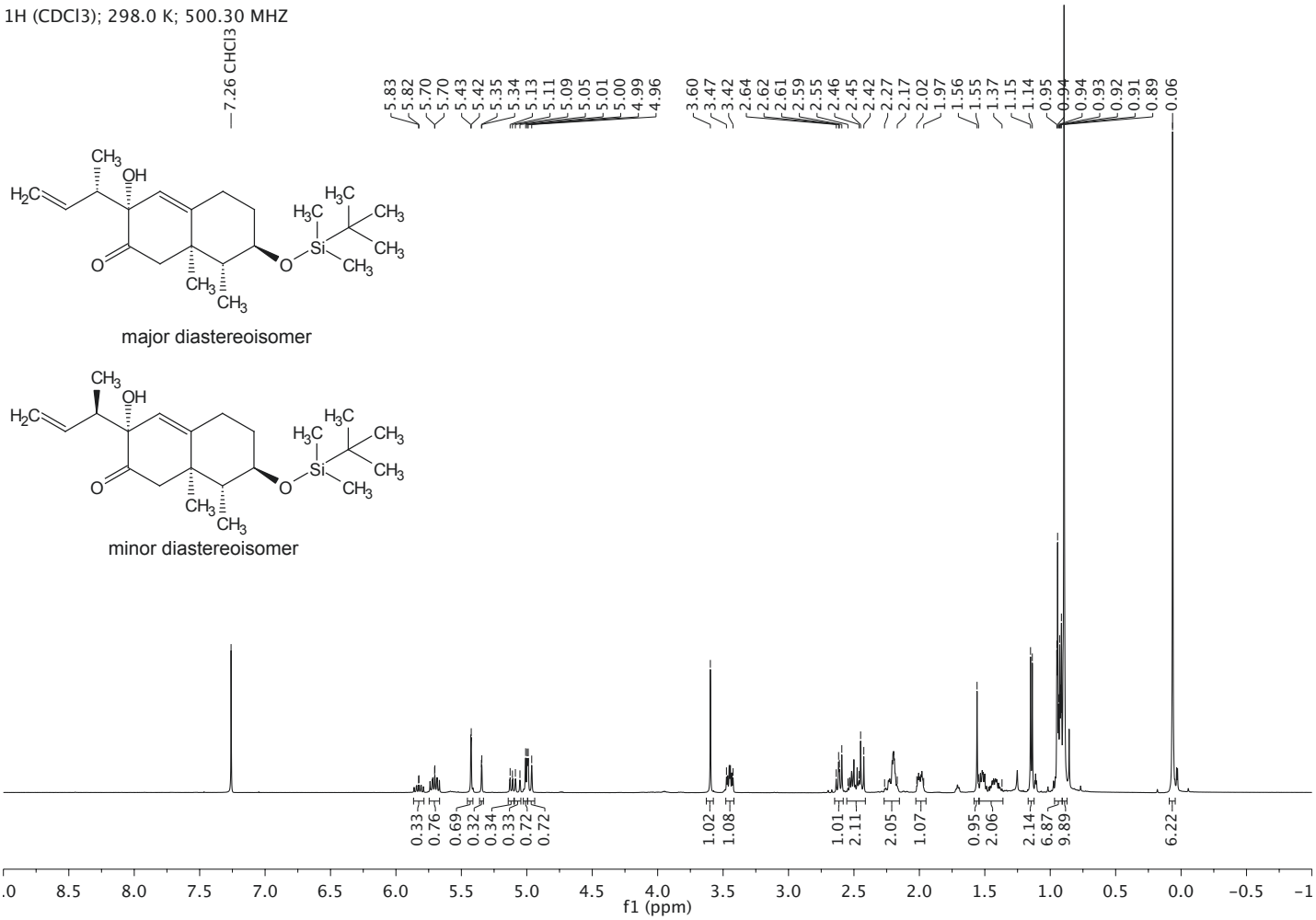
1H (CDCl3); 298.0 K; 500.13 MHZ



13C (CDCl3); 300.0 K; 125.81 MHZ



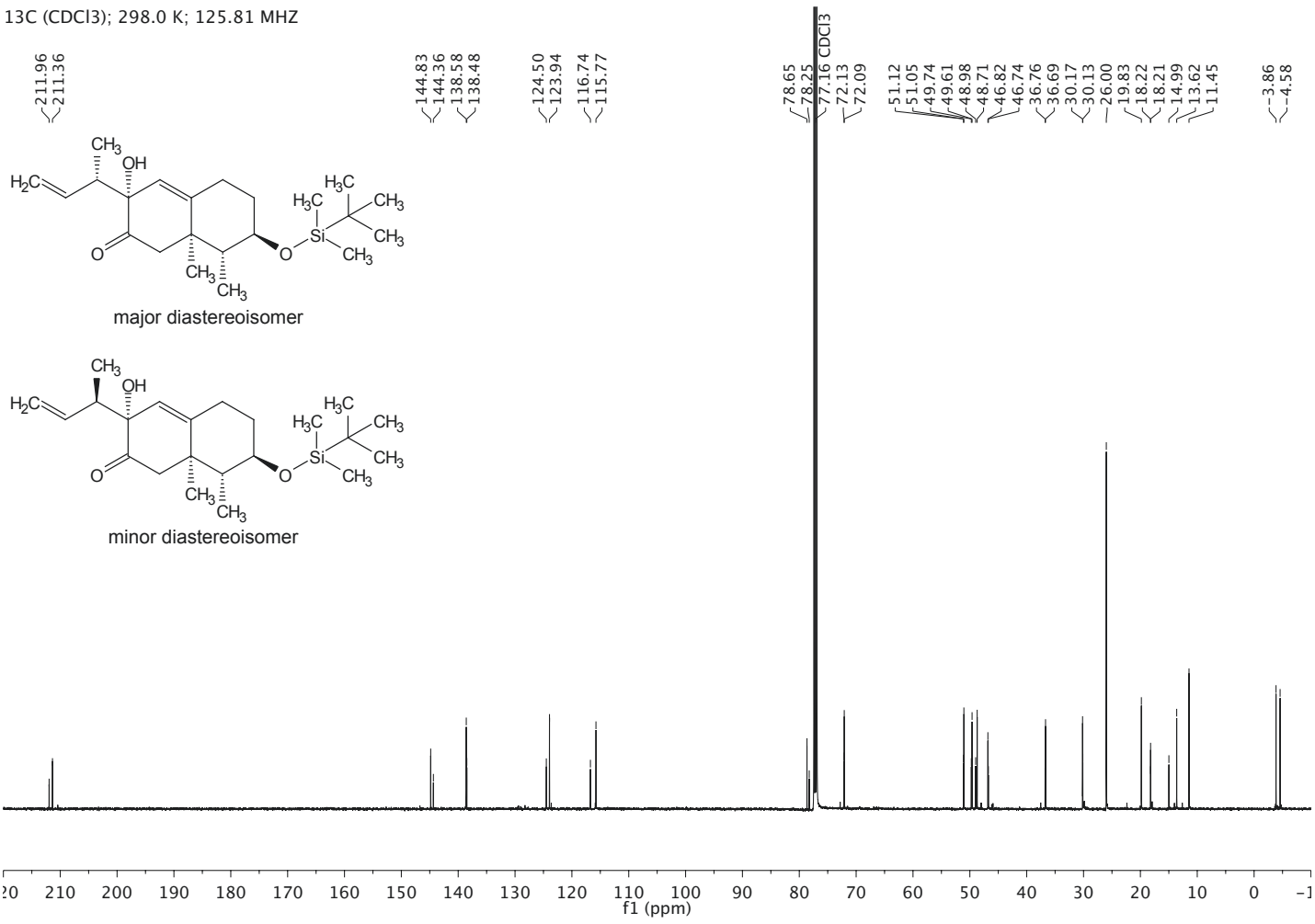
1H (CDCl3); 298.0 K; 500.30 MHZ



major diastereoisomer

minor diastereoisomer

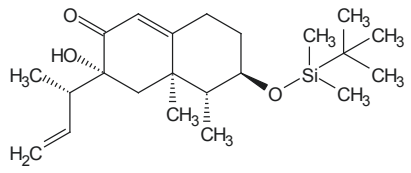
13C (CDCl3); 298.0 K; 125.81 MHZ



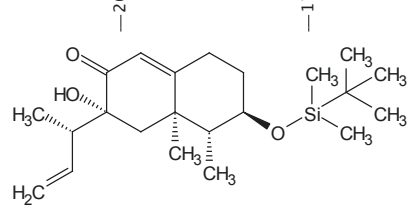
major diastereoisomer

minor diastereoisomer

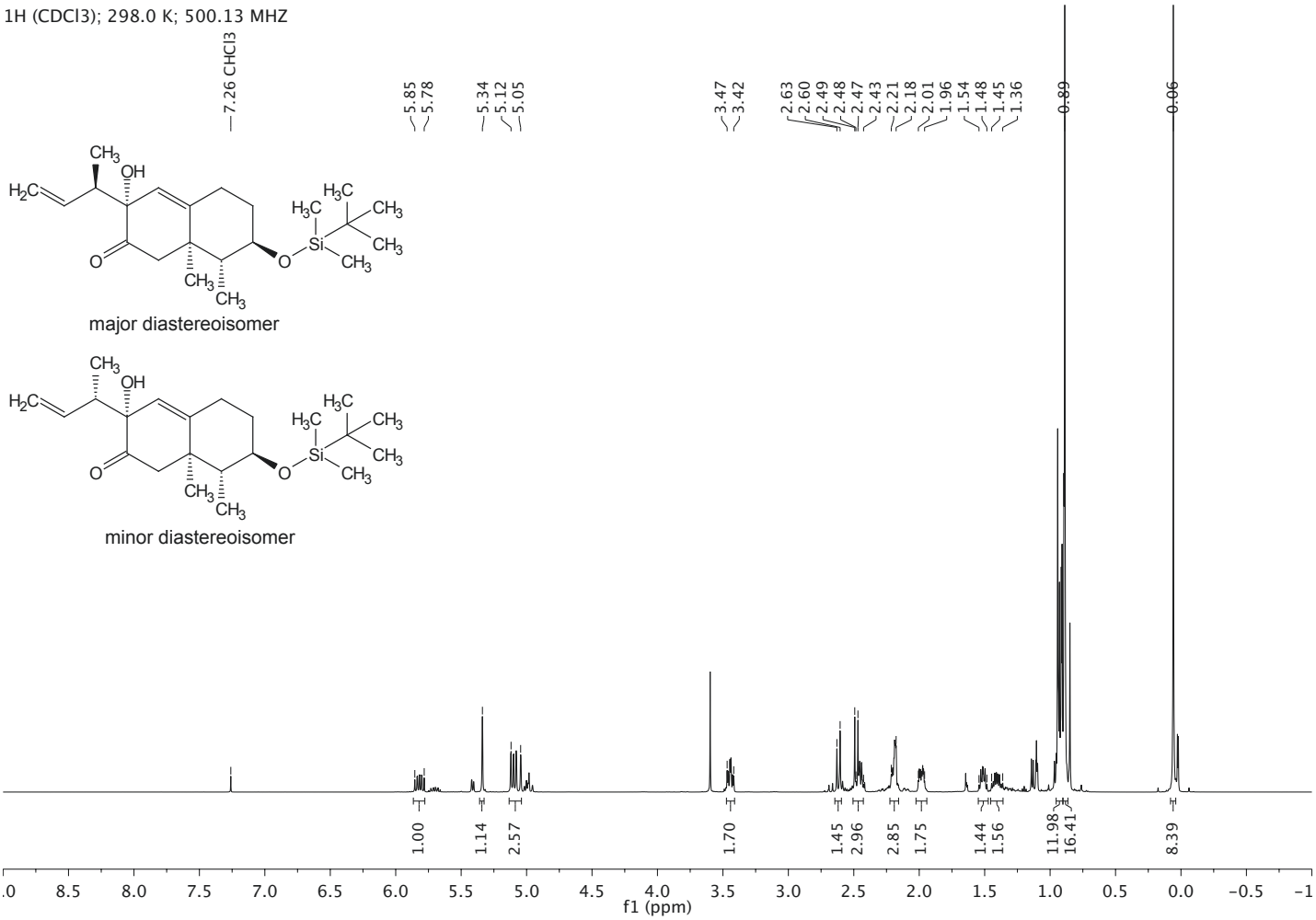
1H (CDCl3); 298.0 K; 500.25 MHZ



13C (CDCl3); 298.1 K; 125.80 MHZ



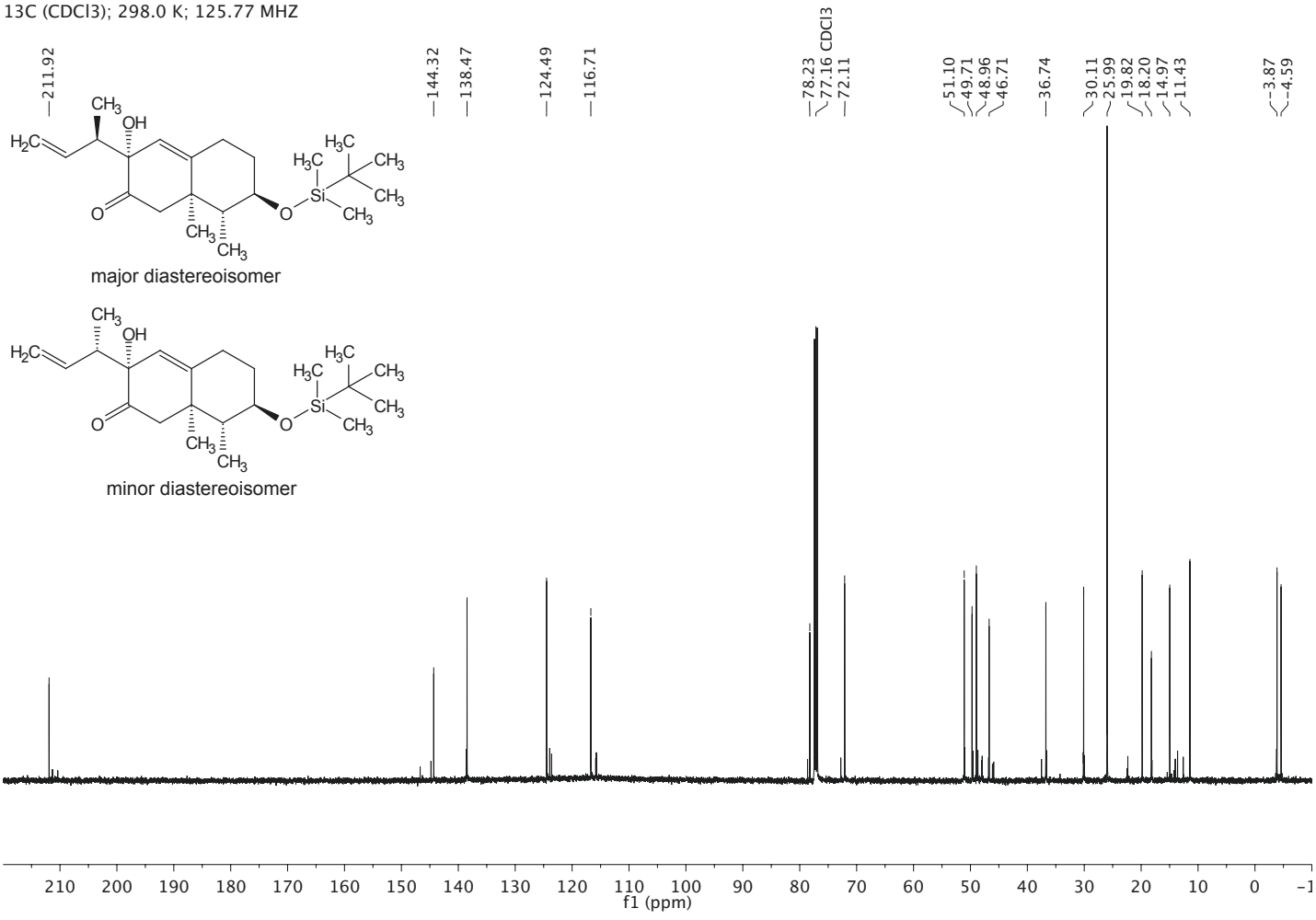
1H (CDCl3); 298.0 K; 500.13 MHZ



major diastereoisomer

minor diastereoisomer

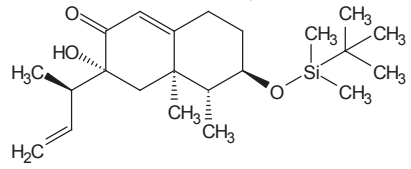
13C (CDCl3); 298.0 K; 125.77 MHZ



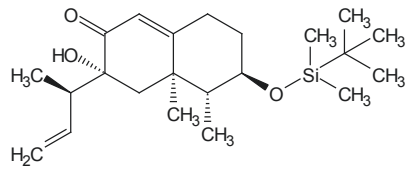
major diastereoisomer

minor diastereoisomer

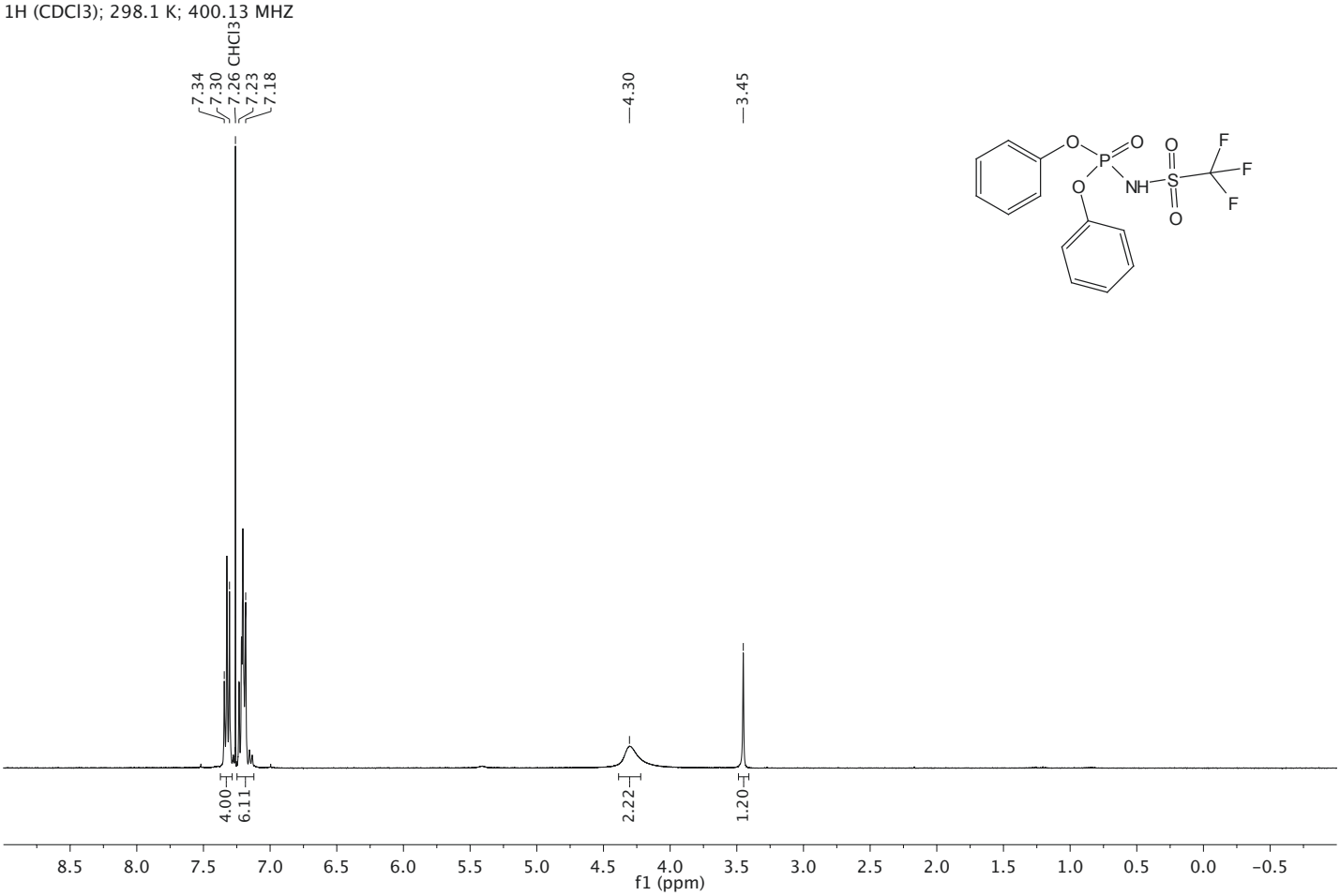
1H (CDCl3); 305.0 K; 400.23 MHZ



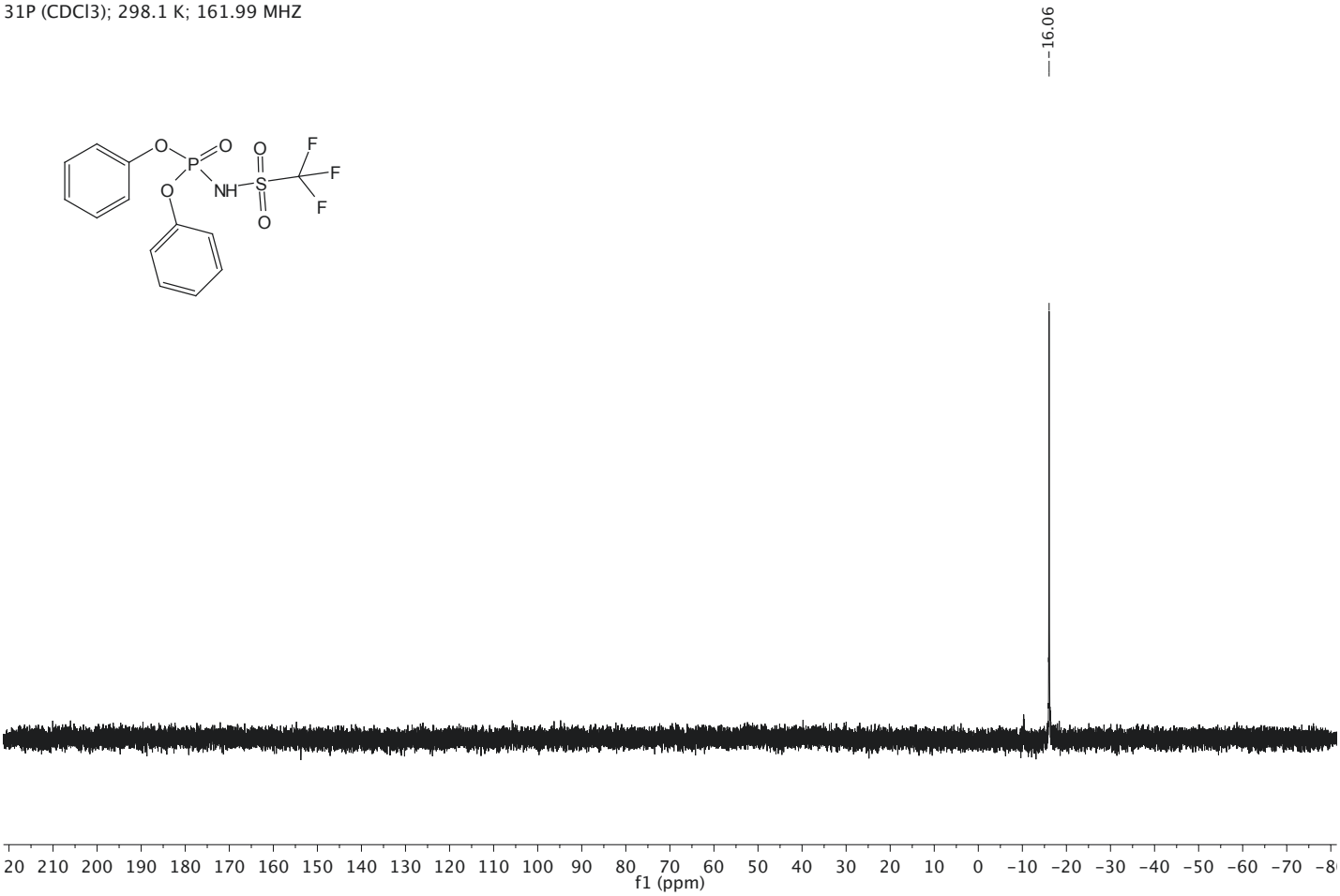
13C (CDCl3); 305.1 K; 100.65 MHZ



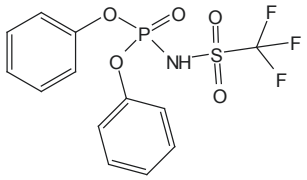
1H (CDCl3); 298.1 K; 400.13 MHZ



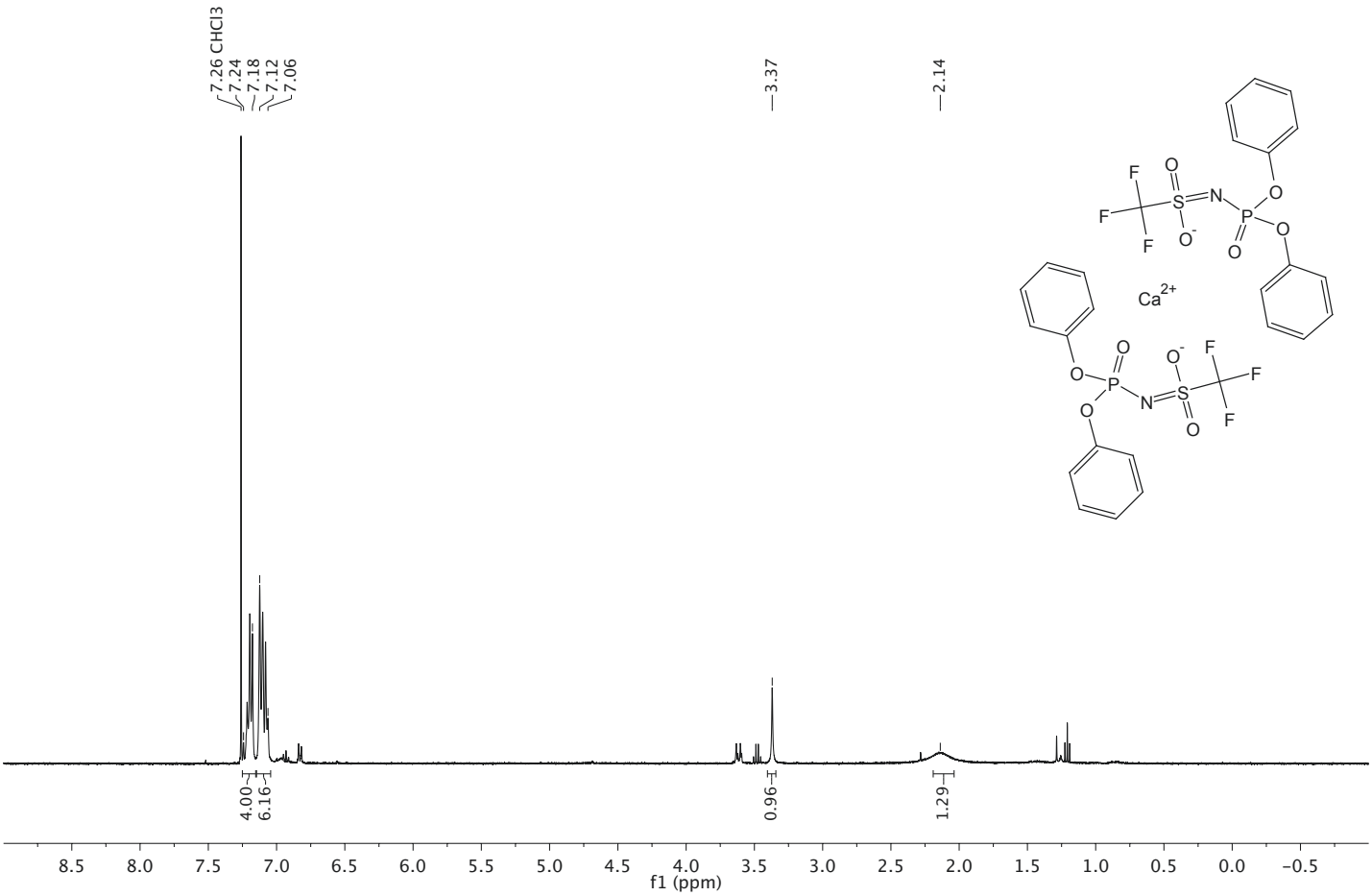
31P (CDCl3); 298.1 K; 161.99 MHZ



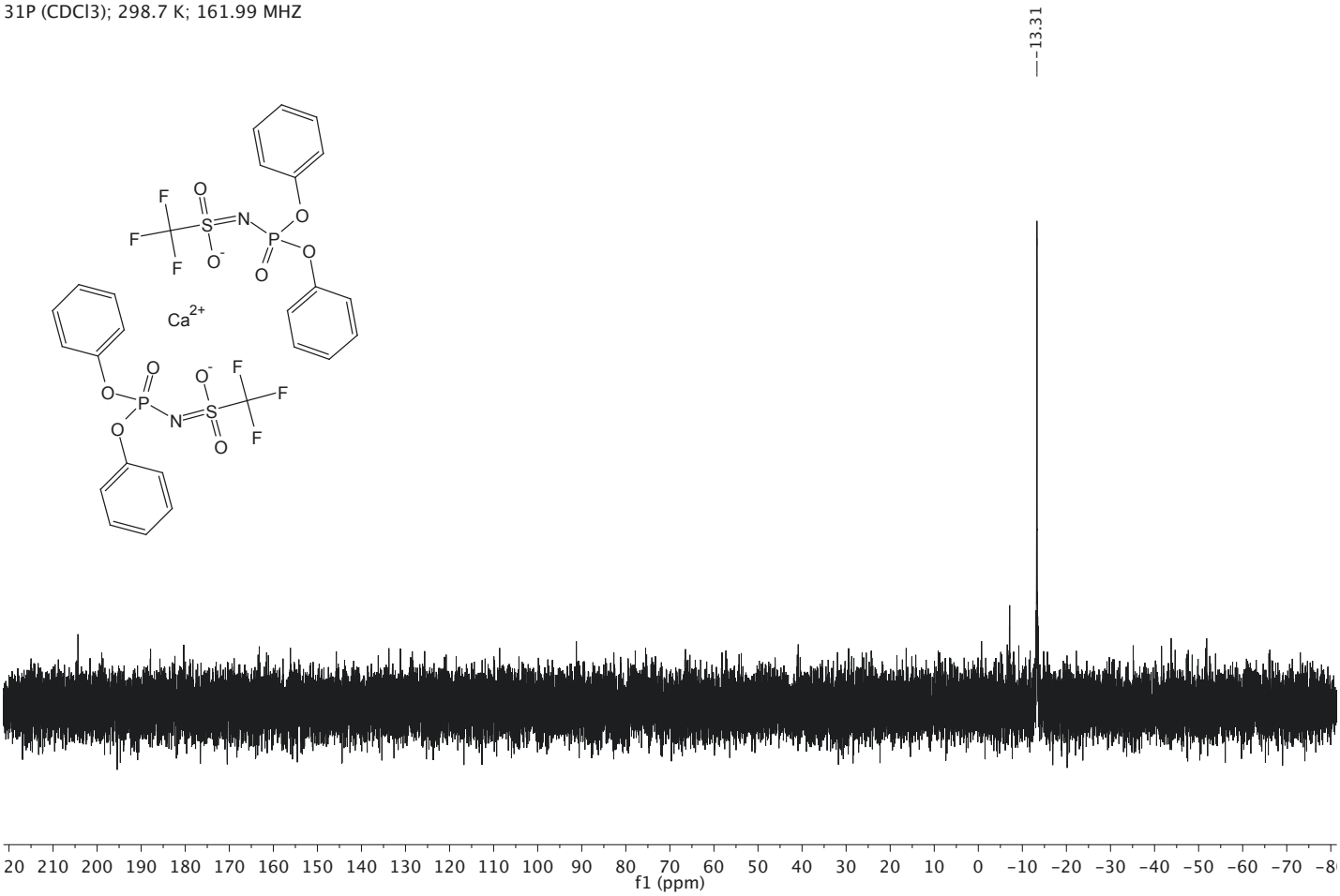
19F (CDCl3); 298.1 K; 376.46 MHZ



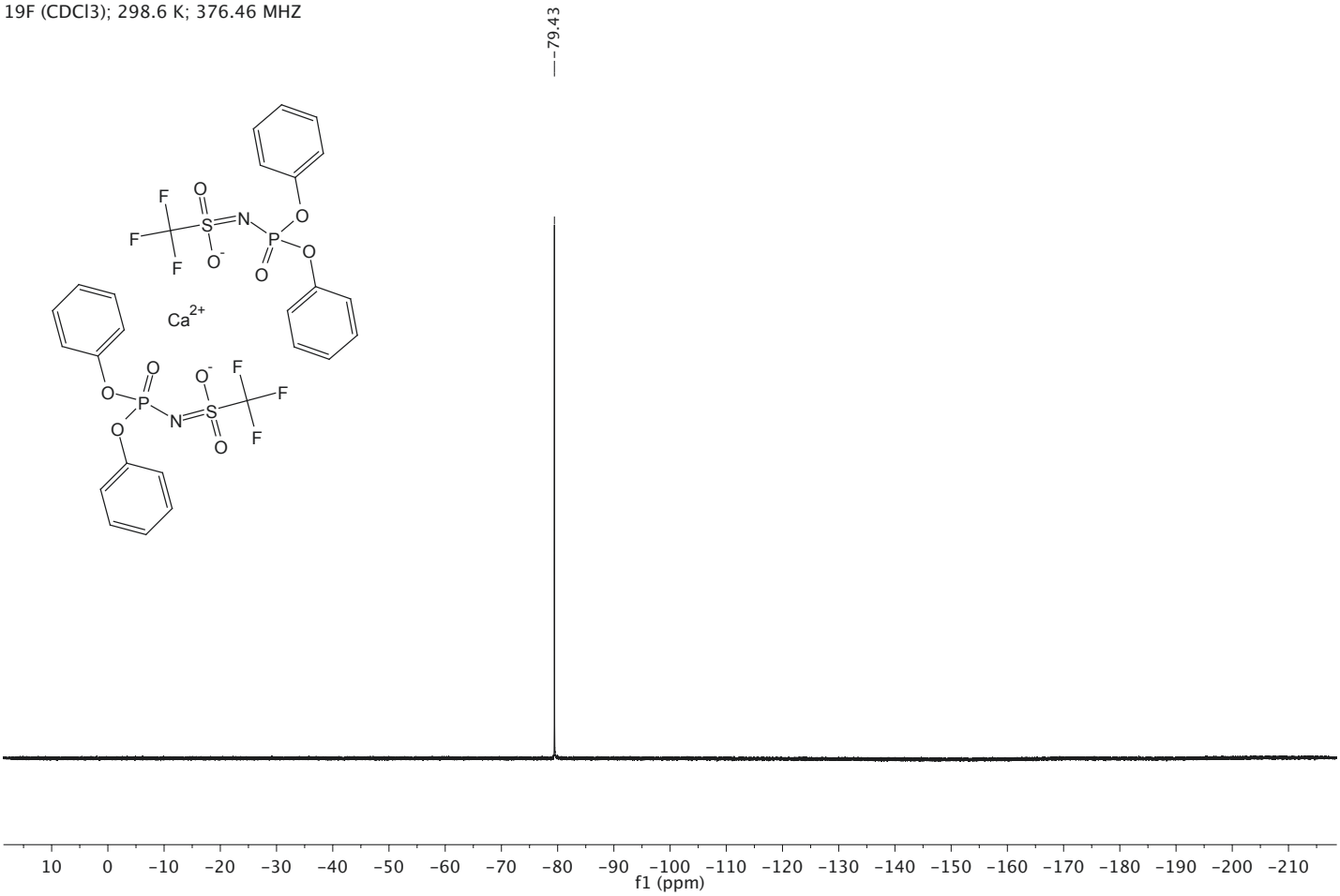
1H (CDCl3); 298.4 K; 400.13 MHZ



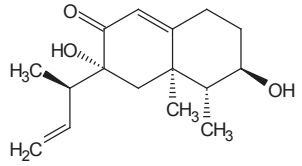
31P (CDCl3); 298.7 K; 161.99 MHZ



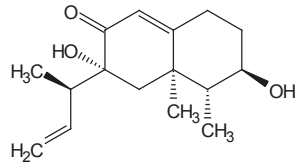
19F (CDCl3); 298.6 K; 376.46 MHZ



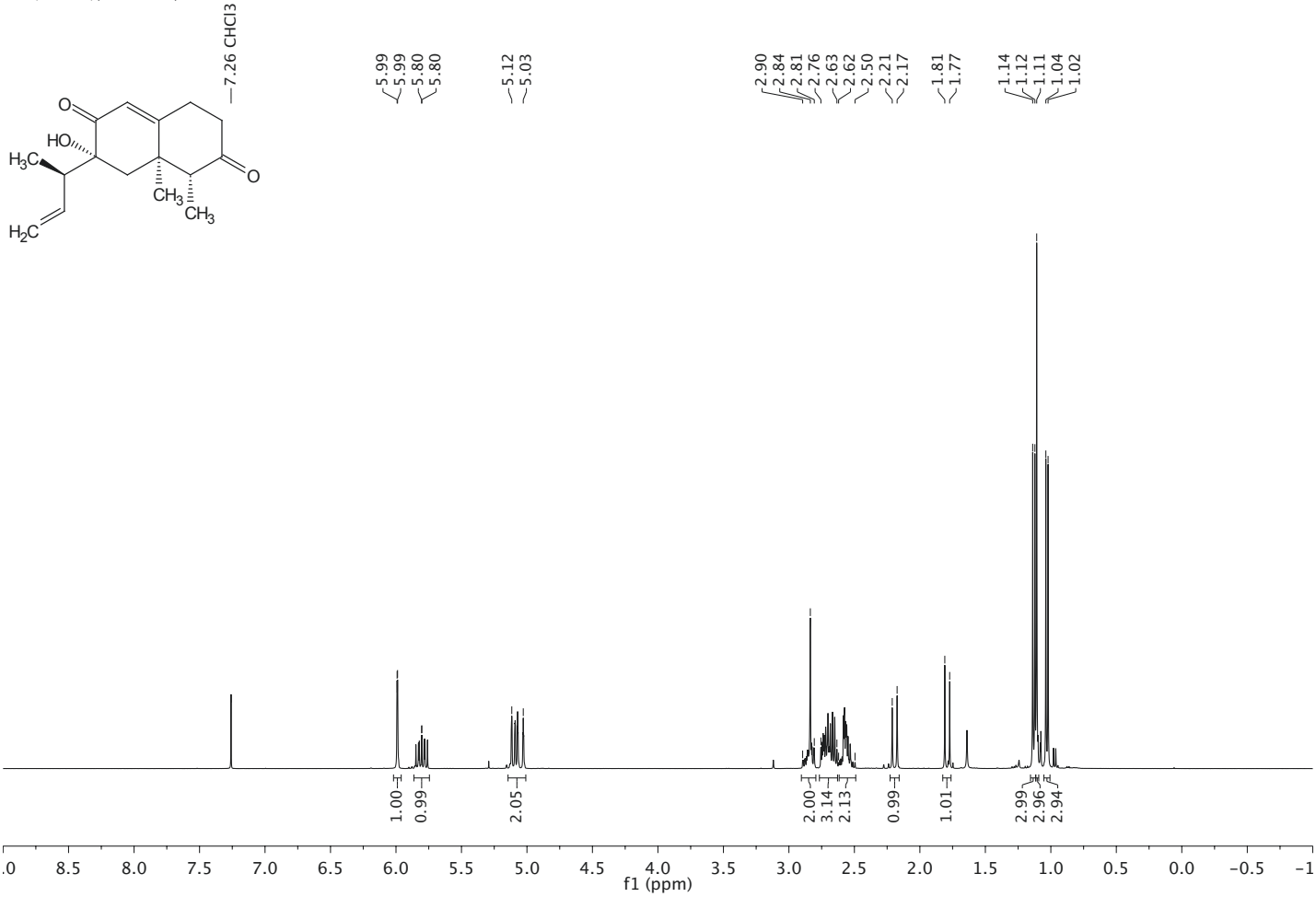
1H (CDCl3); 300.0 K; 400.23 MHZ



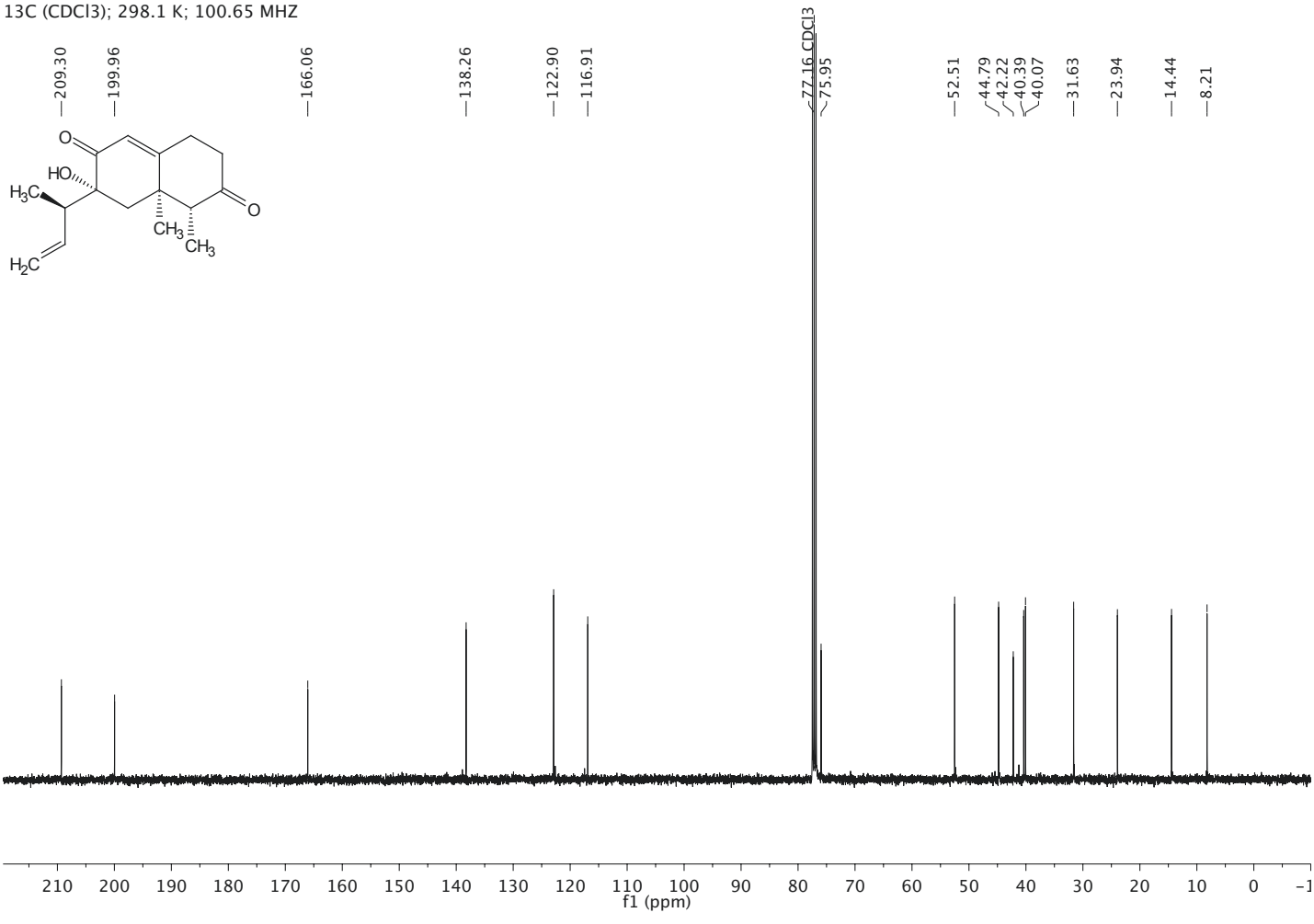
13C (CDCl3); 300.0 K; 100.65 MHZ



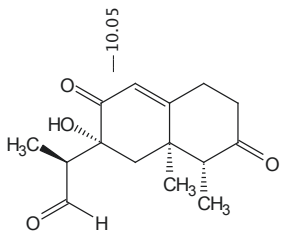
1H (CDCl3); 298.0 K; 400.23 MHZ



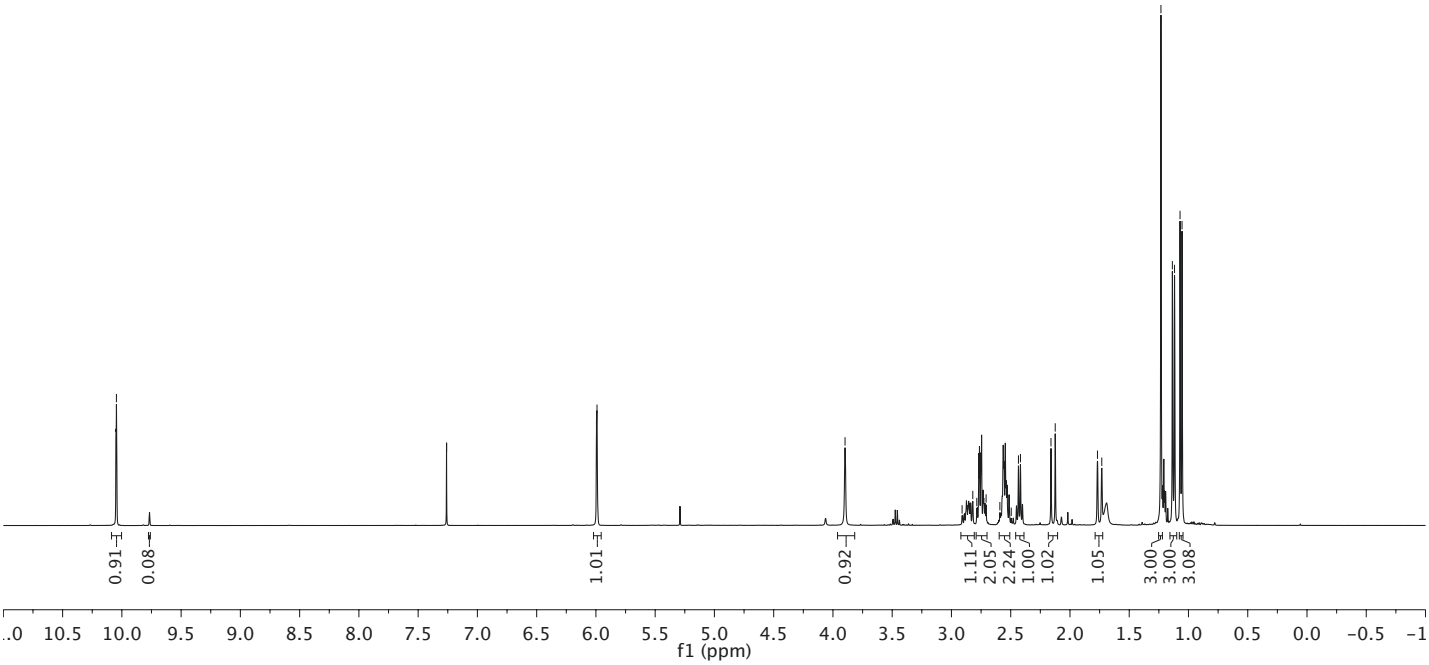
13C (CDCl3); 298.1 K; 100.65 MHZ



1H (CDCl3); 298.0 K; 400.23 MHZ

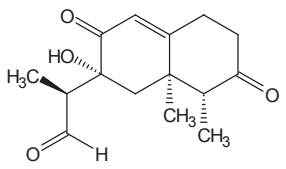


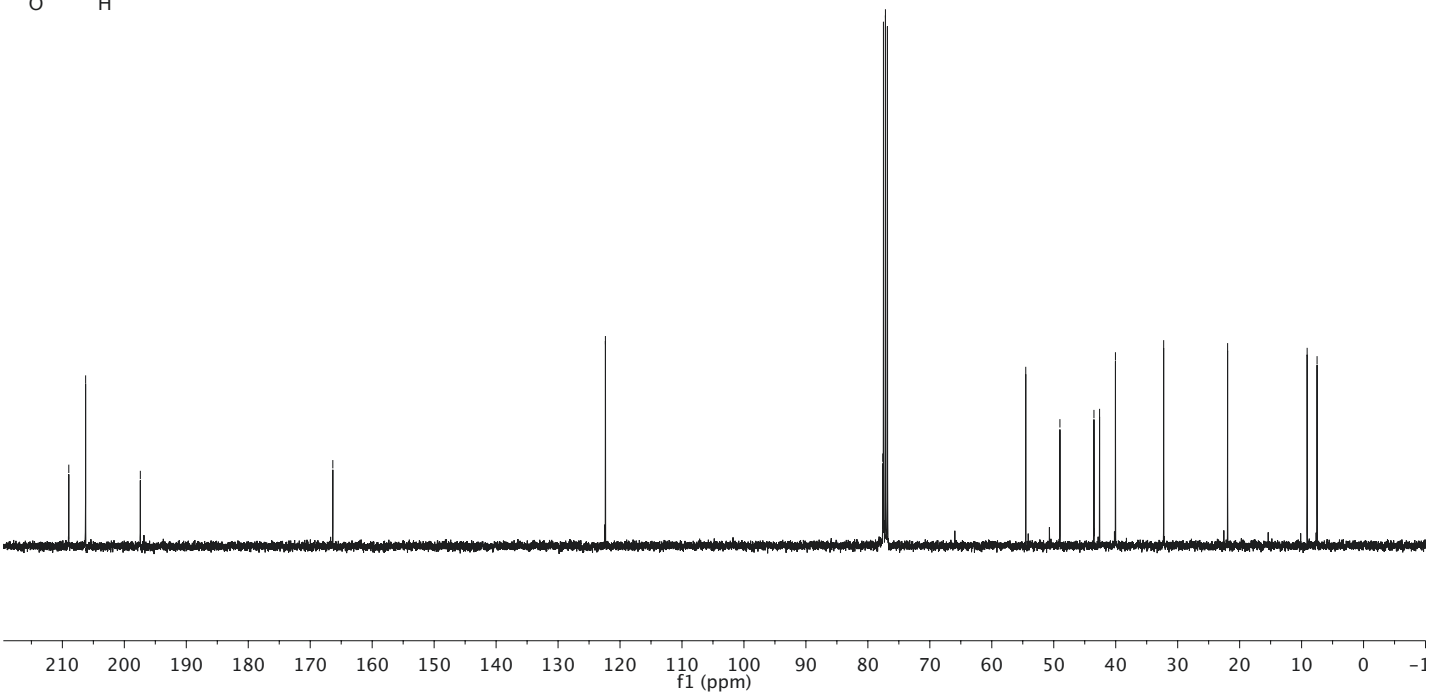
10.05 | 7.26 CHCl3 | 6.00 | 5.99 | 3.90 | 2.91 | 2.82 | 2.79 | 2.71 | 2.59 | 2.50 | 2.43 | 2.42 | 2.16 | 2.12 | 1.77 | 1.73 | 1.23 | 1.14 | 1.12 | 1.07 | 1.05



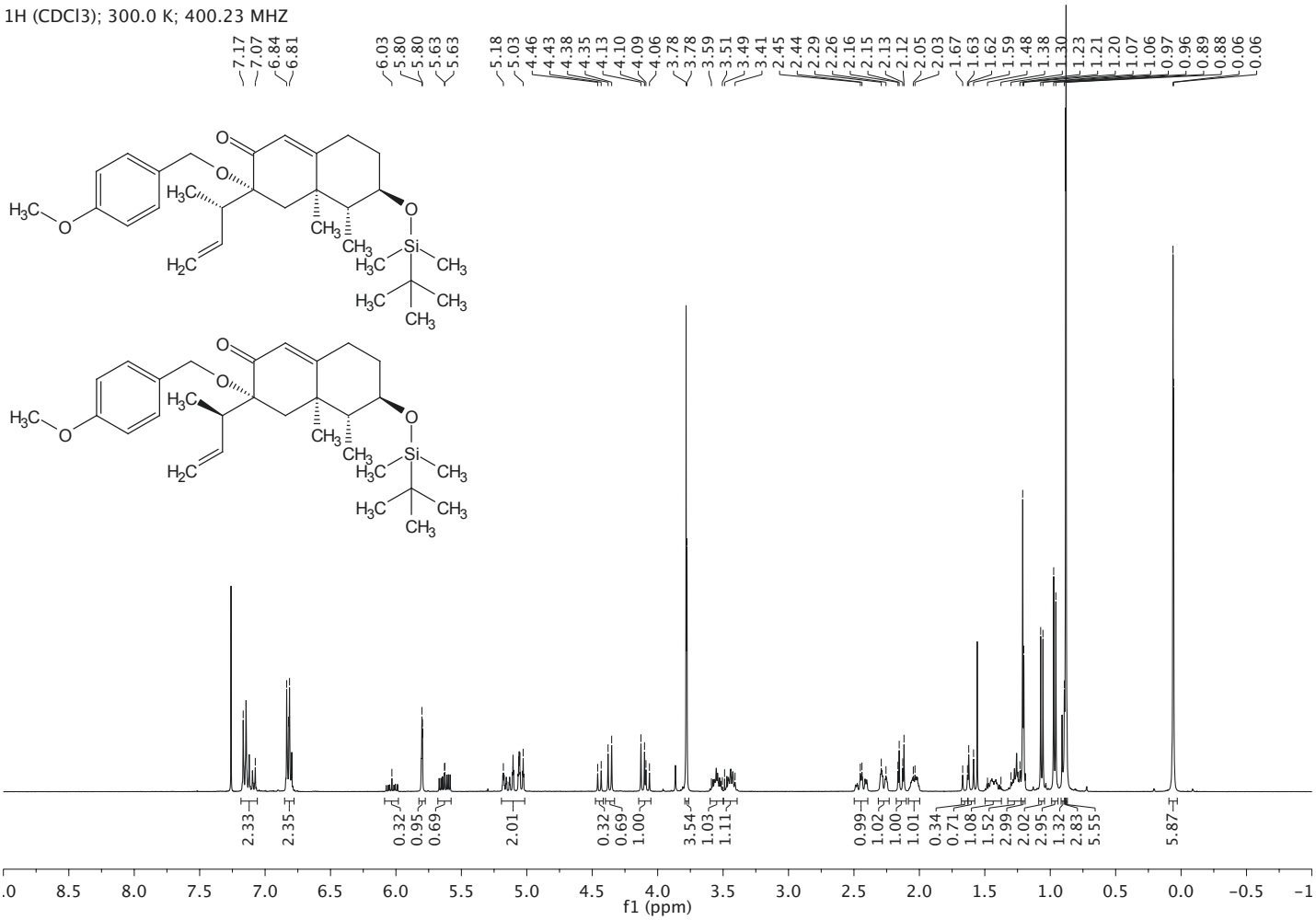
13C (CDCl3); 298.1 K; 100.65 MHZ

208.97 | 206.25 | 197.42 | 166.35 | 122.36 | 77.60 | 77.16 CDCl3 | 54.52 | 49.00 | 43.51 | 42.61 | 40.04 | 32.26 | 21.94 | 9.10 | 7.50

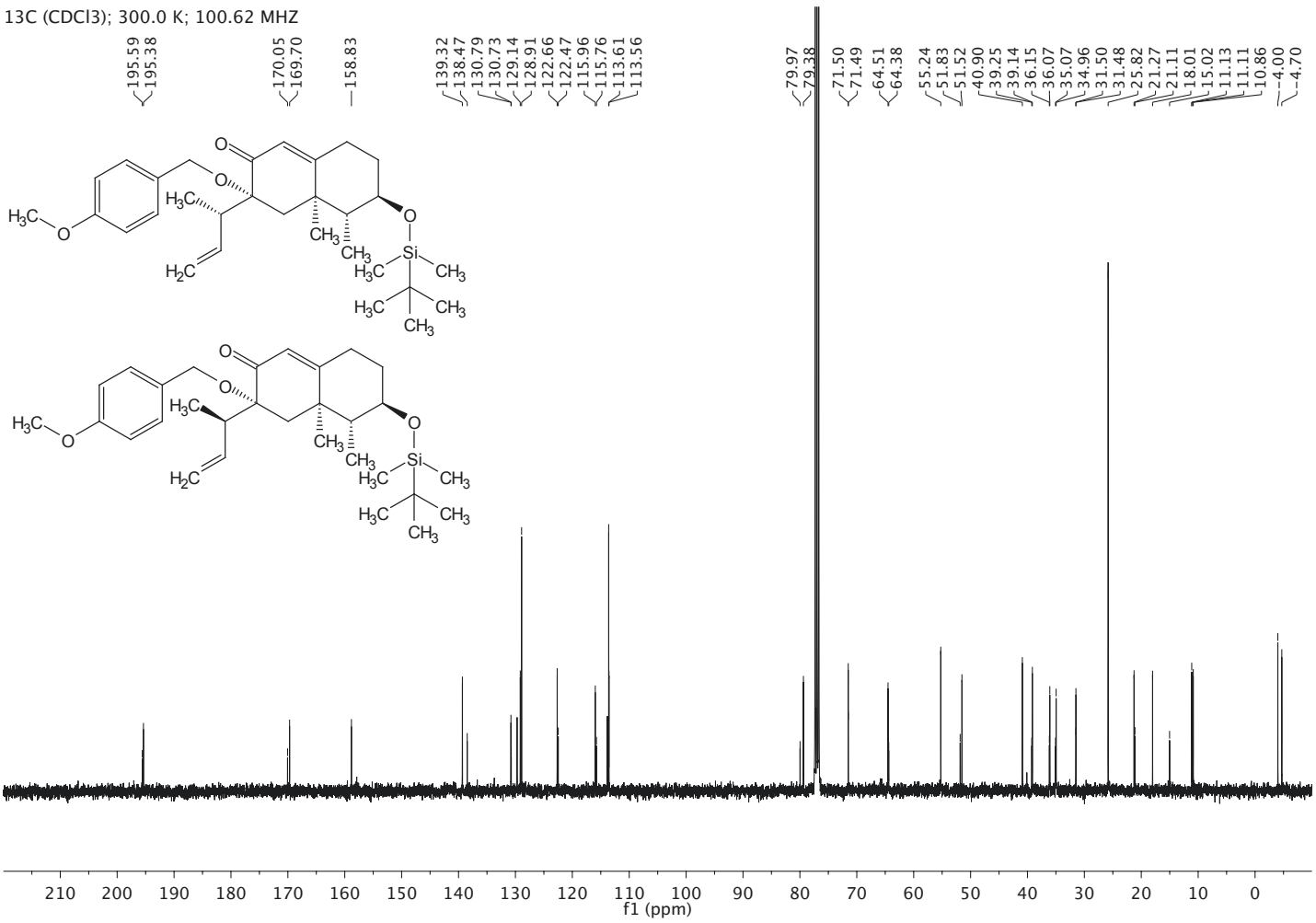




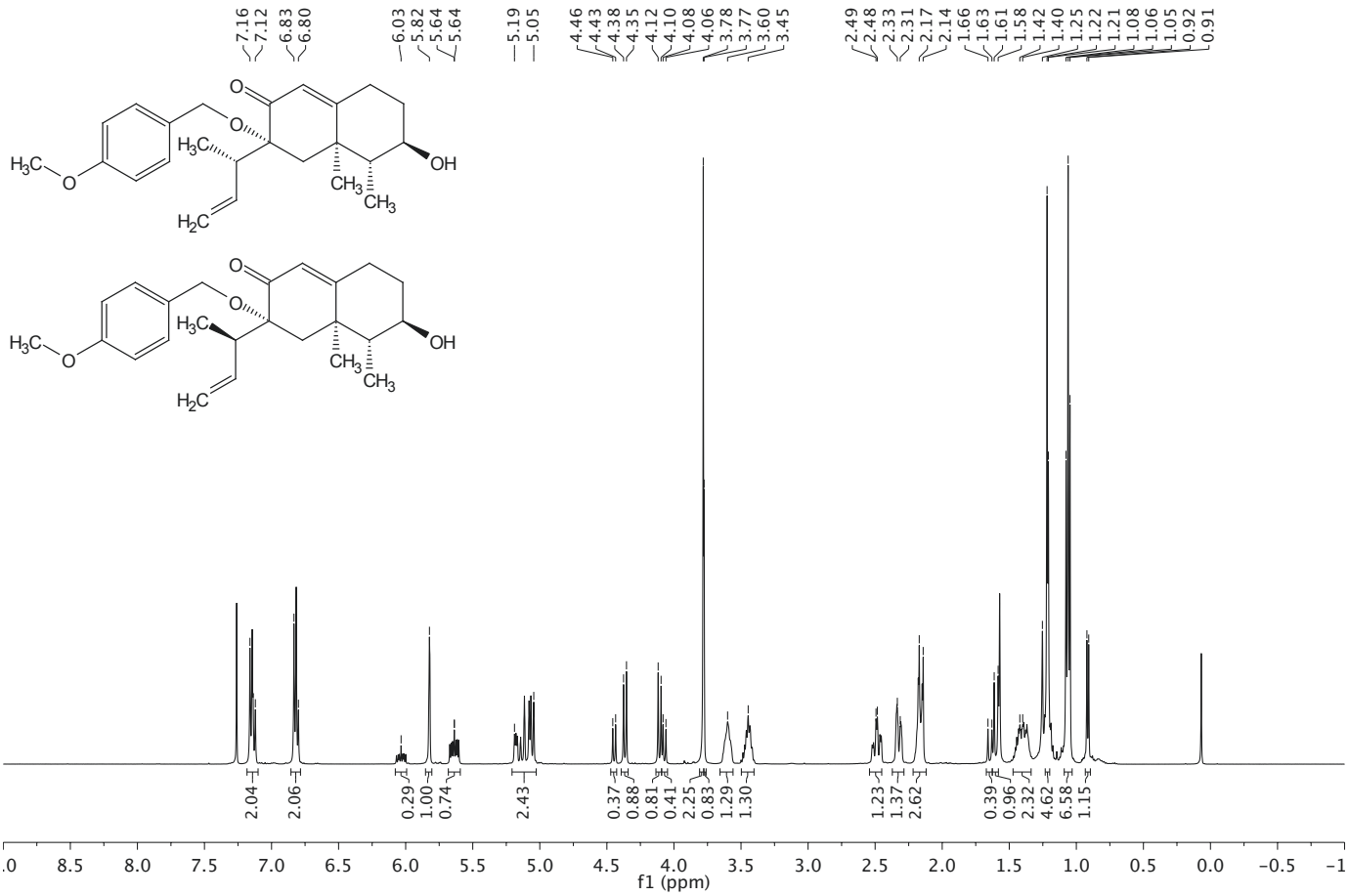
1H (CDCl3); 300.0 K; 400.23 MHZ



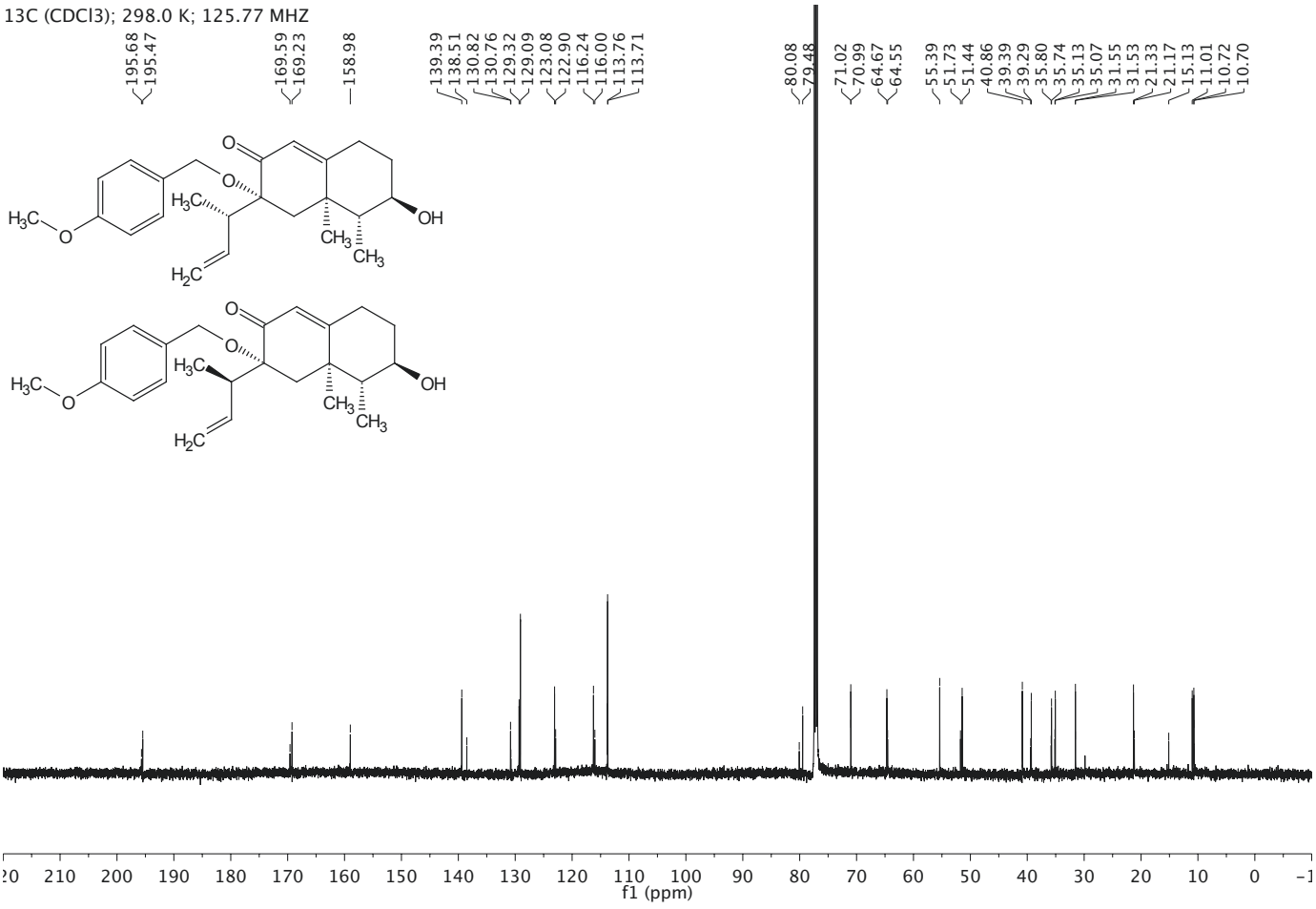
13C (CDCl3); 300.0 K; 100.62 MHZ



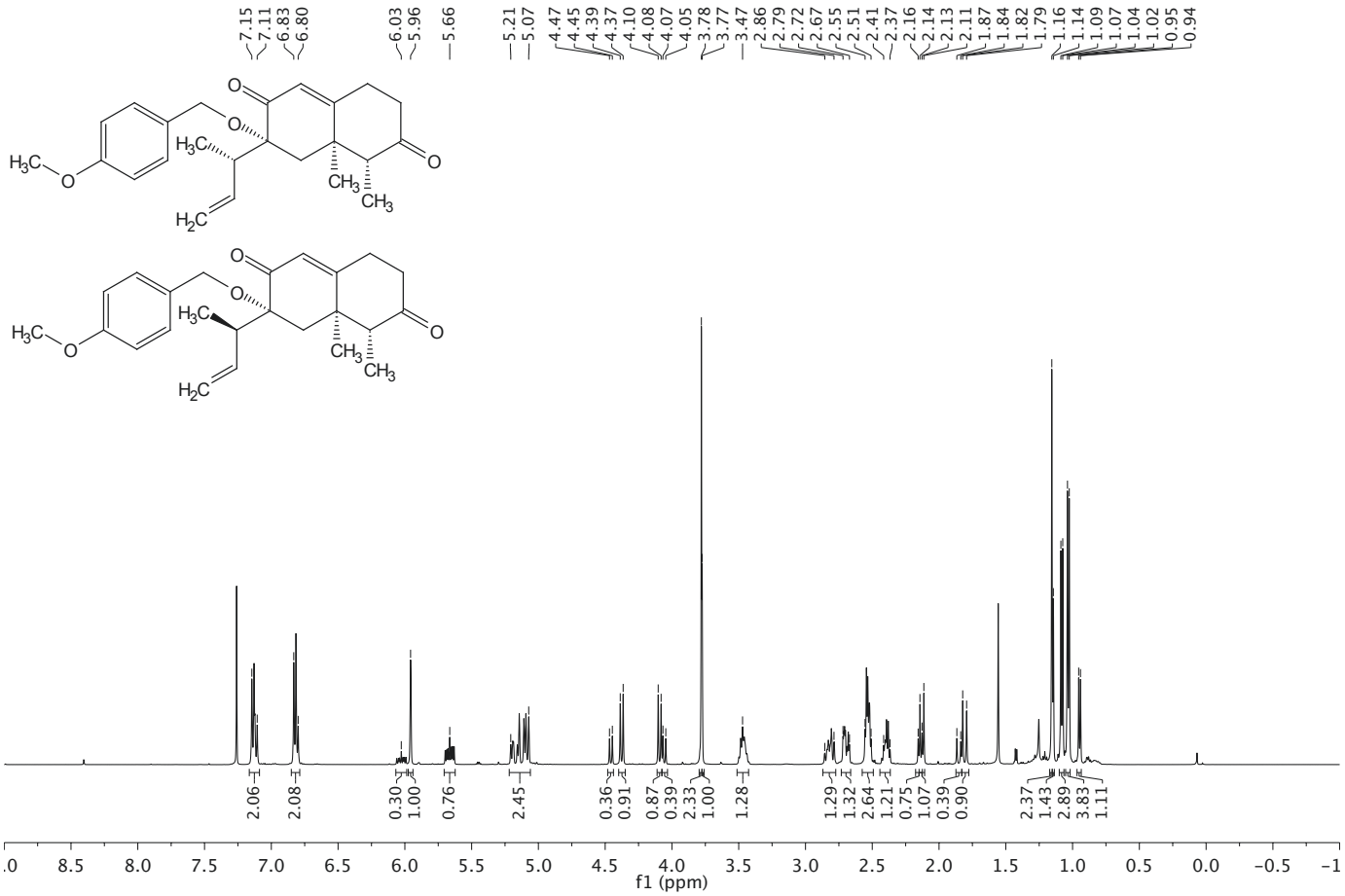
1H (CDCl3); 298.0 K; 500.13 MHZ



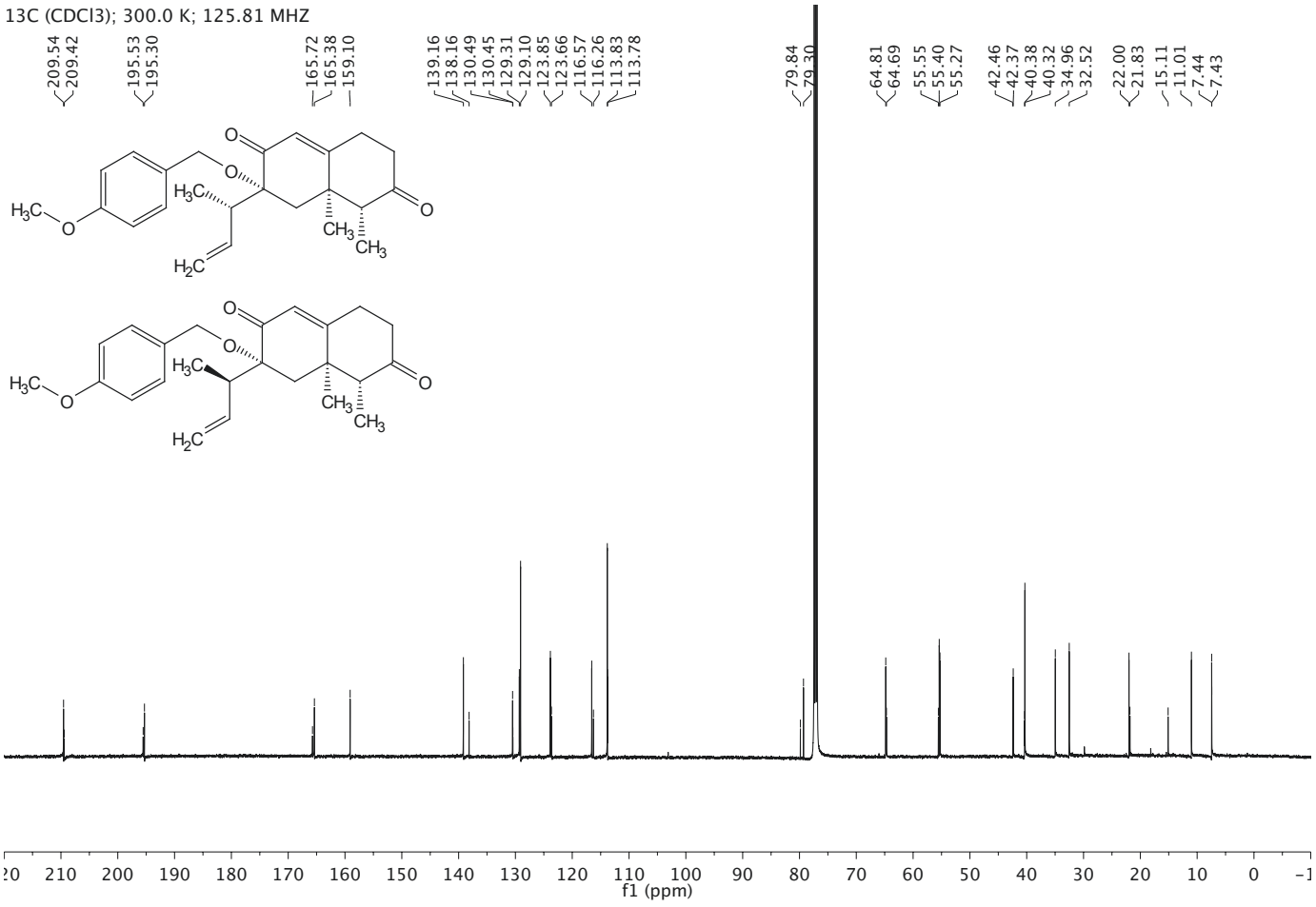
13C (CDCl3); 298.0 K; 125.77 MHZ



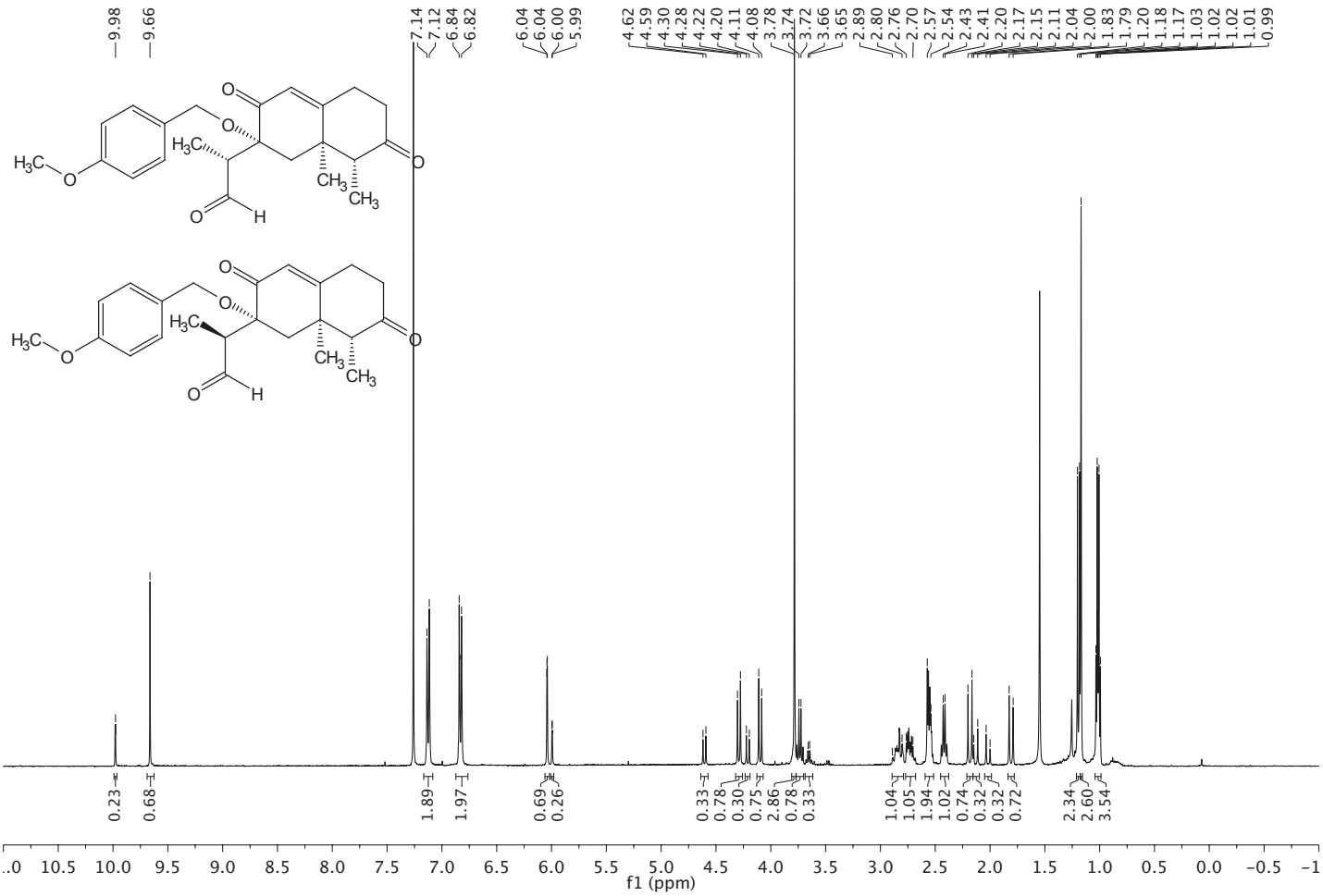
1H (CDCl3); 298.0 K; 500.13 MHZ



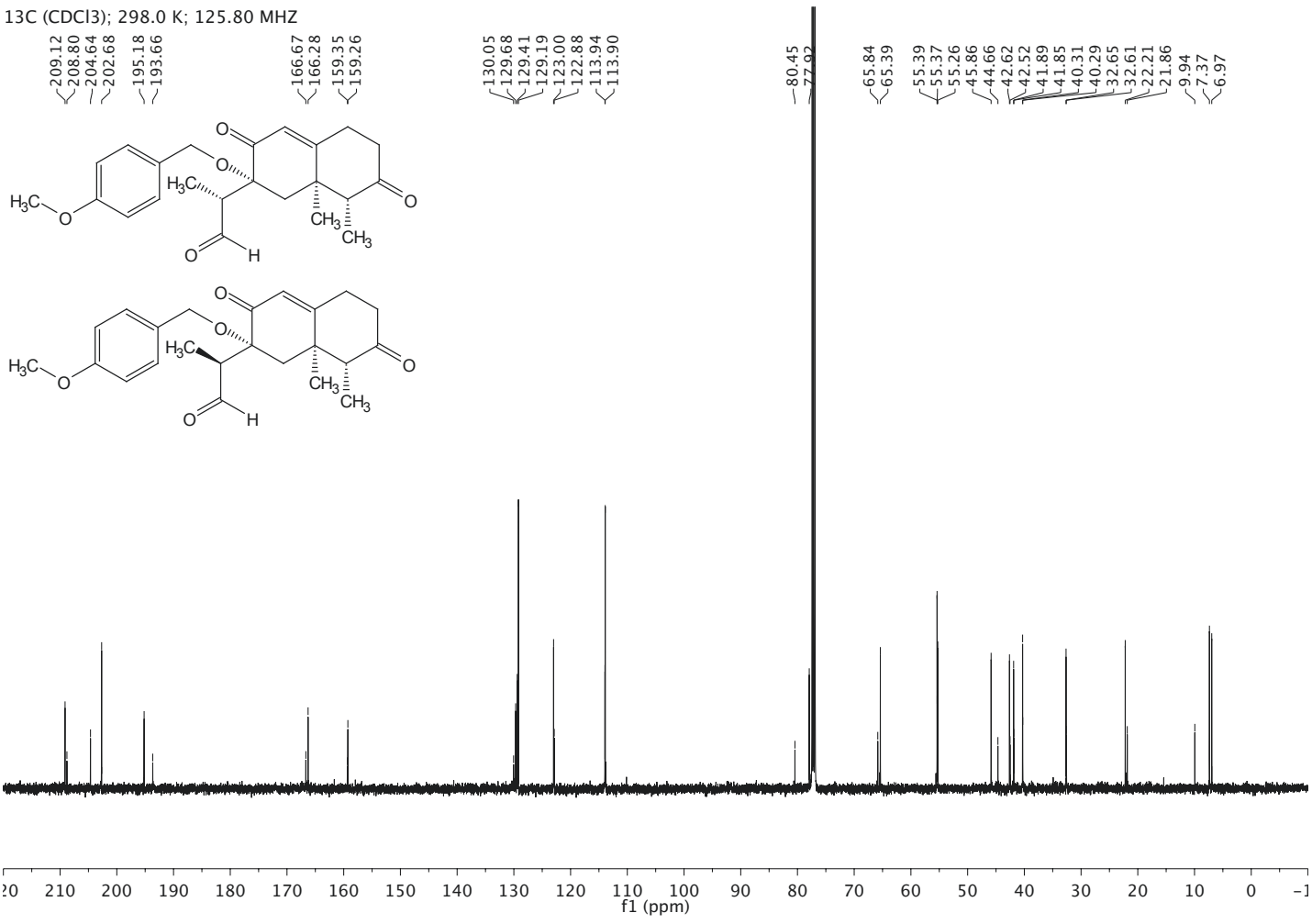
13C (CDCl3); 300.0 K; 125.81 MHZ



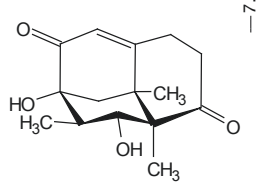
1H (CDCl3); 300.0 K; 400.23 MHZ



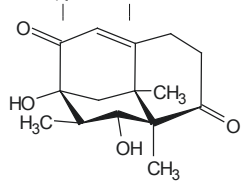
13C (CDCl3); 298.0 K; 125.80 MHZ



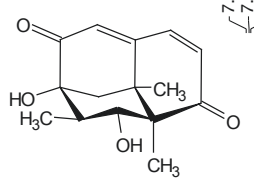
1H (CDCl3); 298.0 K; 500.25 MHZ



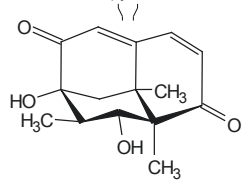
13C (CDCl3); 298.0 K; 125.80 MHZ



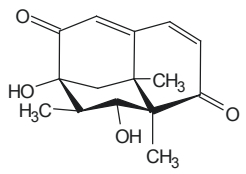
1H (CDCl3); 309.9 K; 500.25 MHZ



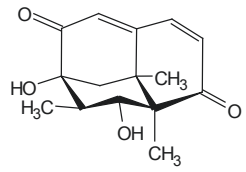
13C (CDCl3); 298.0 K; 125.80 MHZ



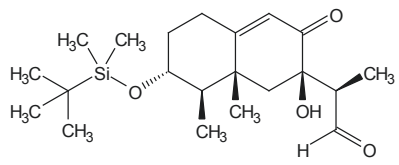
1H (DMSO); 308.1 K; 500.30 MHZ



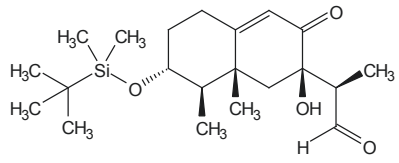
13C (DMSO); 300.0 K; 125.81 MHZ



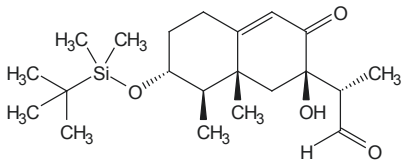
1H (CDCl3); 300.0 K; 400.23 MHZ



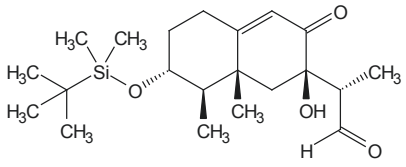
13C (CDCl3); 300.0 K; 125.81 MHZ



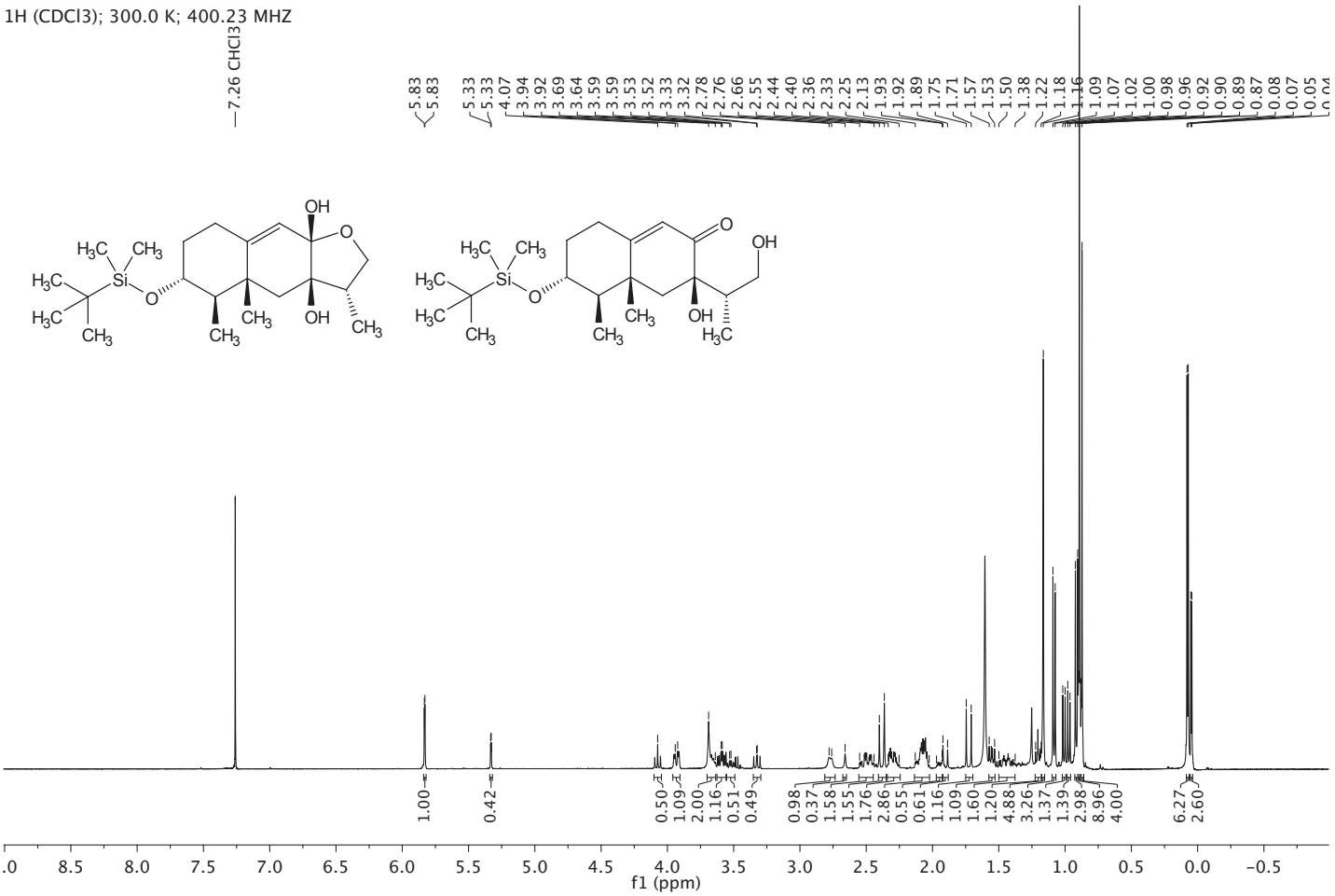
1H (CDCl3); 300.0 K; 400.23 MHZ



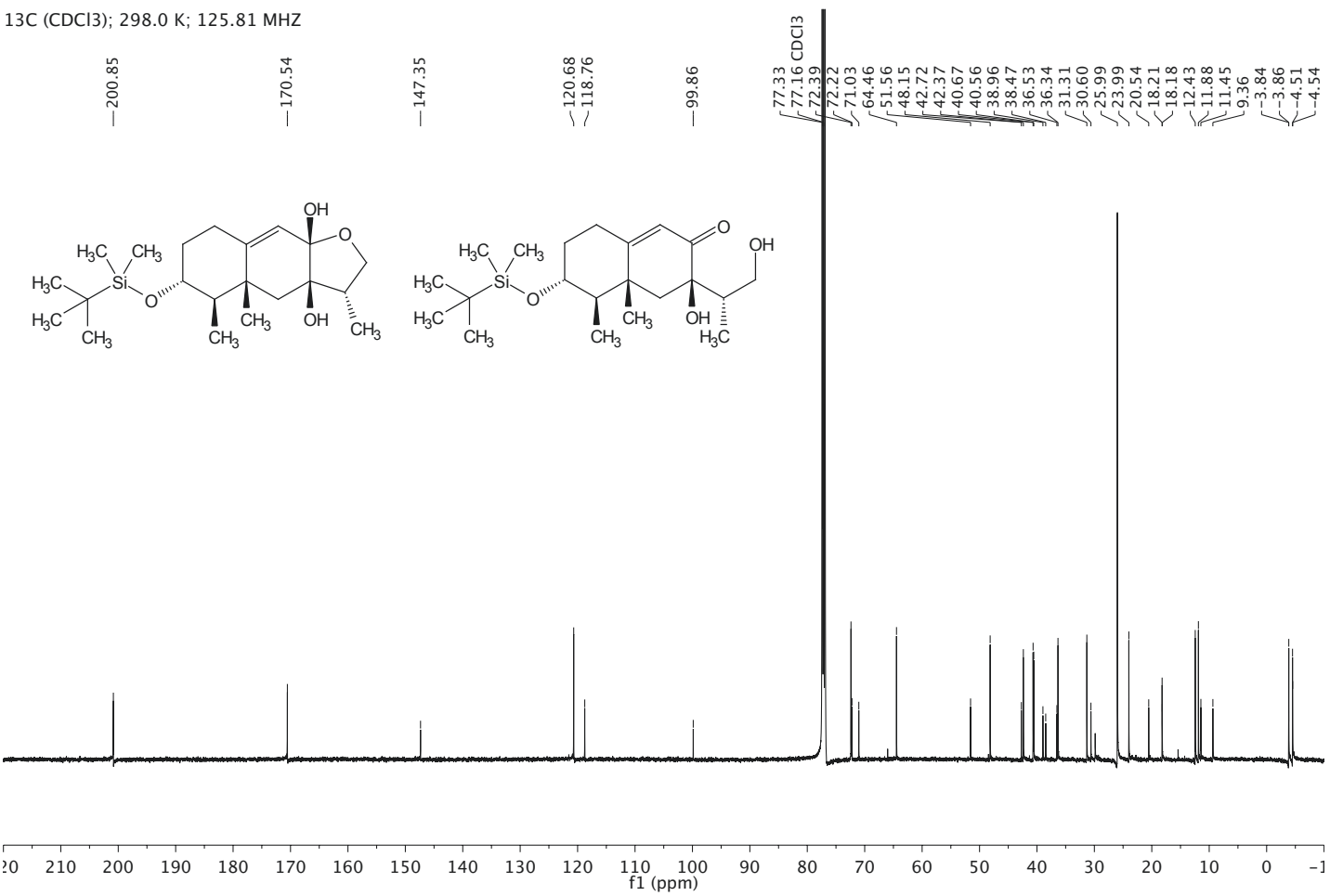
13C (CDCl3); 300.0 K; 125.81 MHZ



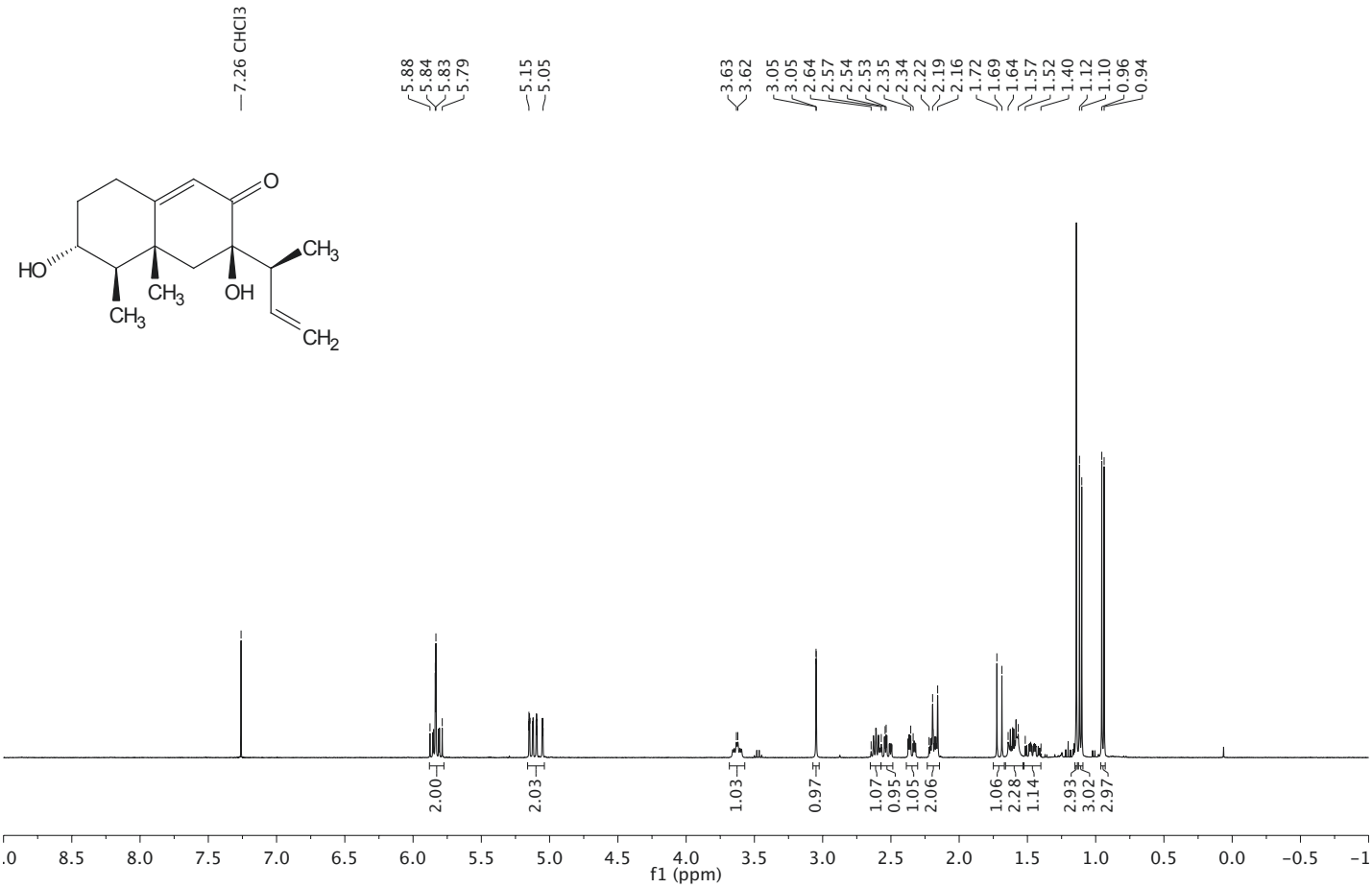
1H (CDCl3); 300.0 K; 400.23 MHZ



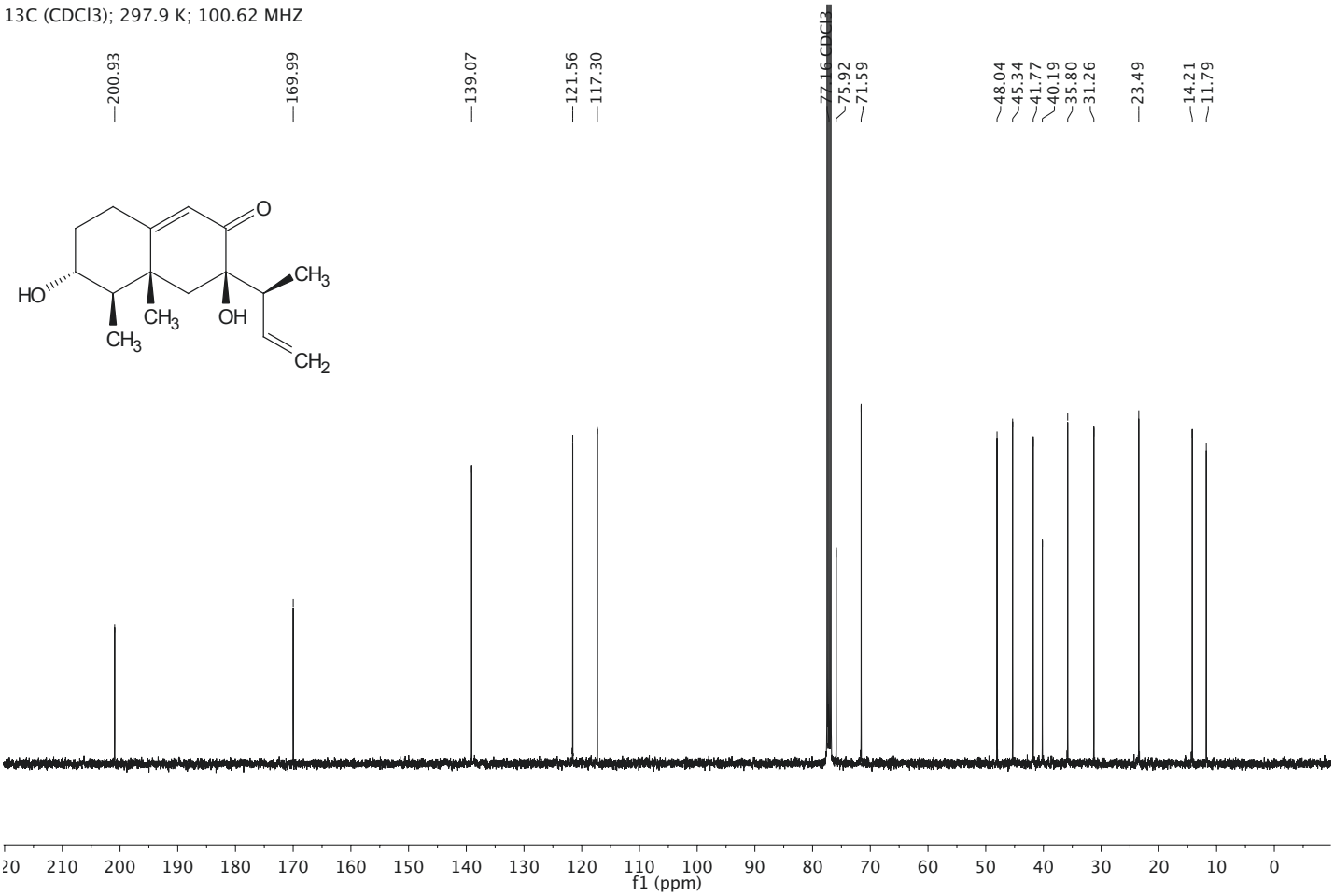
13C (CDCl3); 298.0 K; 125.81 MHZ



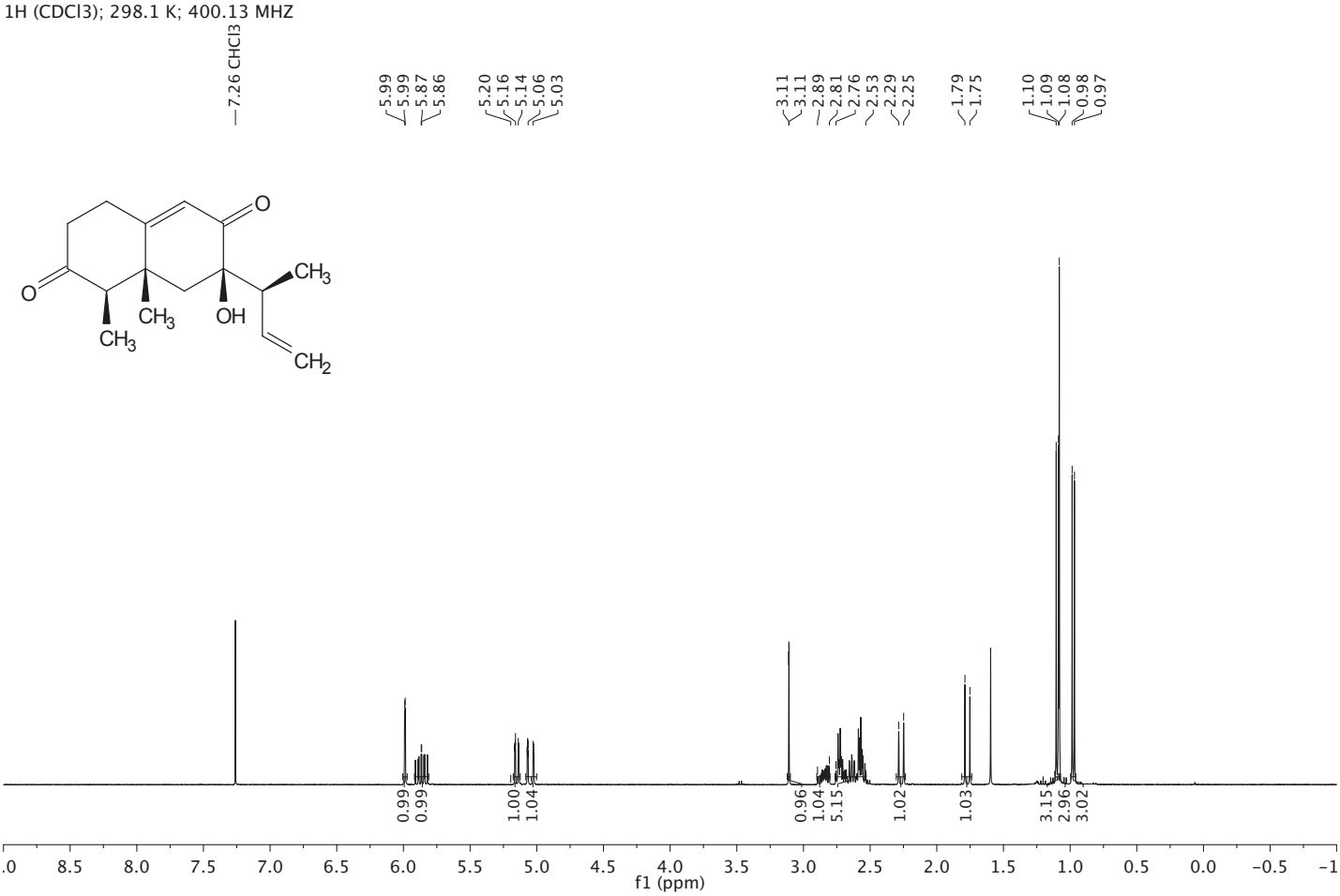
1H (CDCl3); 298.1 K; 400.13 MHZ



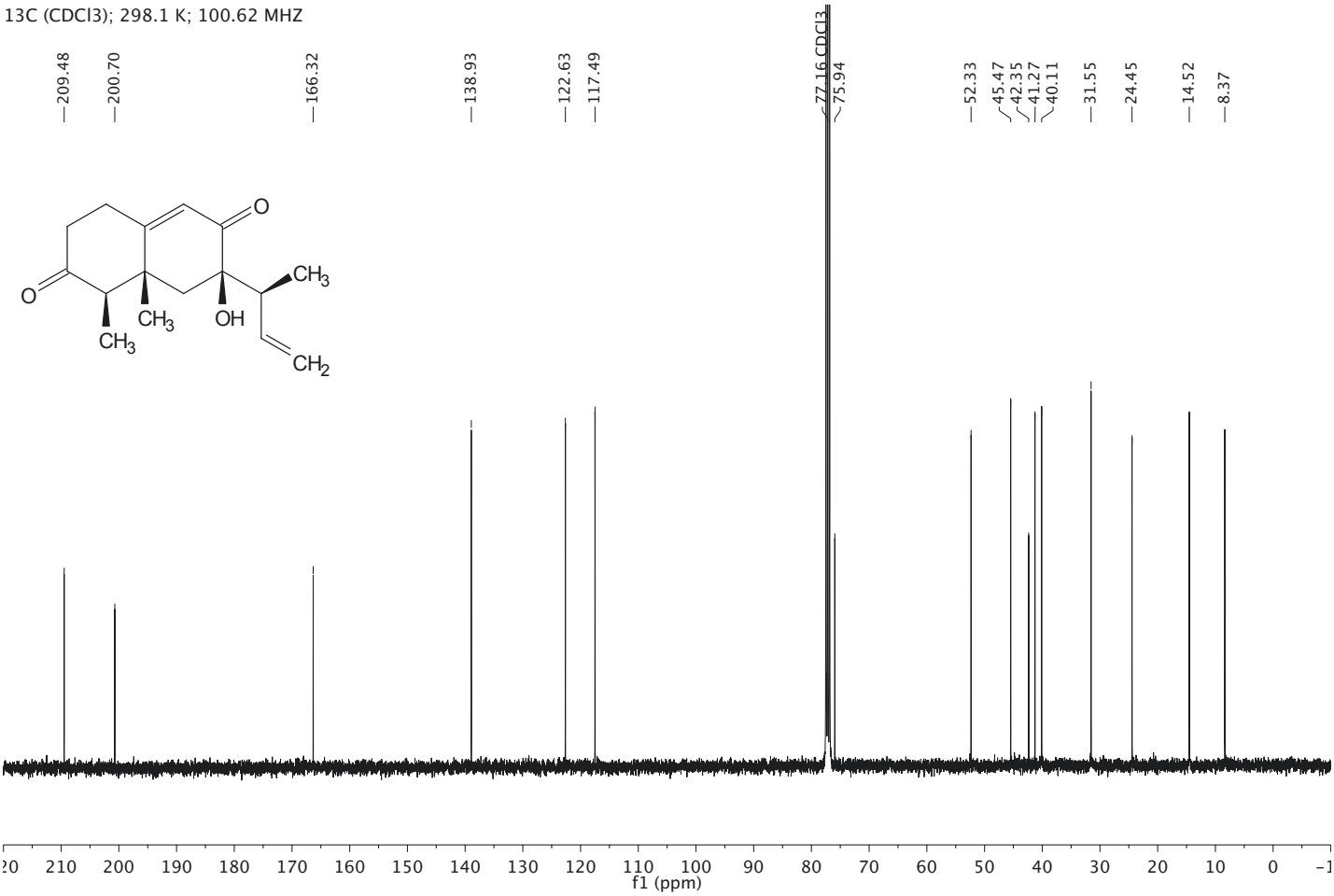
13C (CDCl3); 297.9 K; 100.62 MHZ



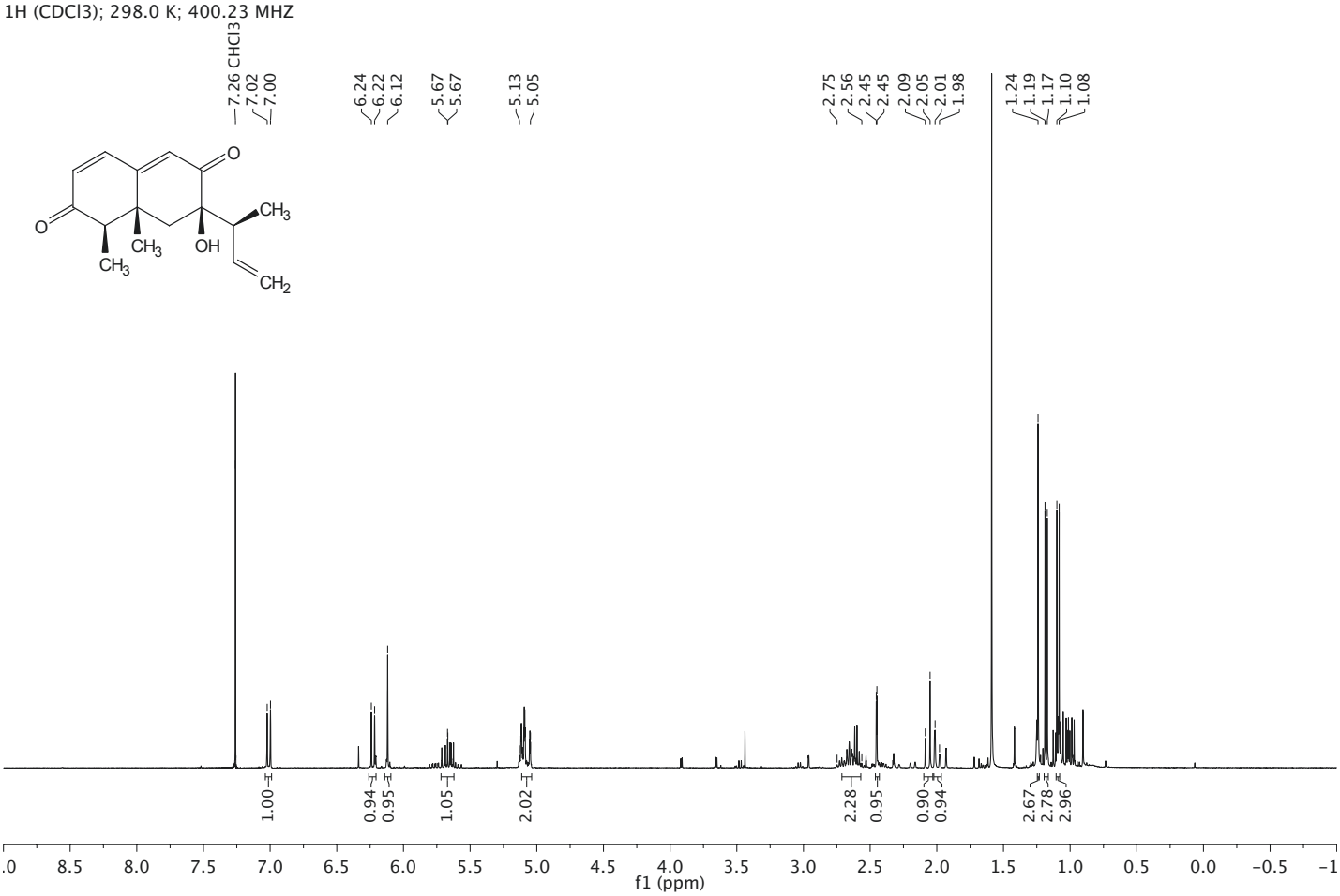
1H (CDCl3); 298.1 K; 400.13 MHZ



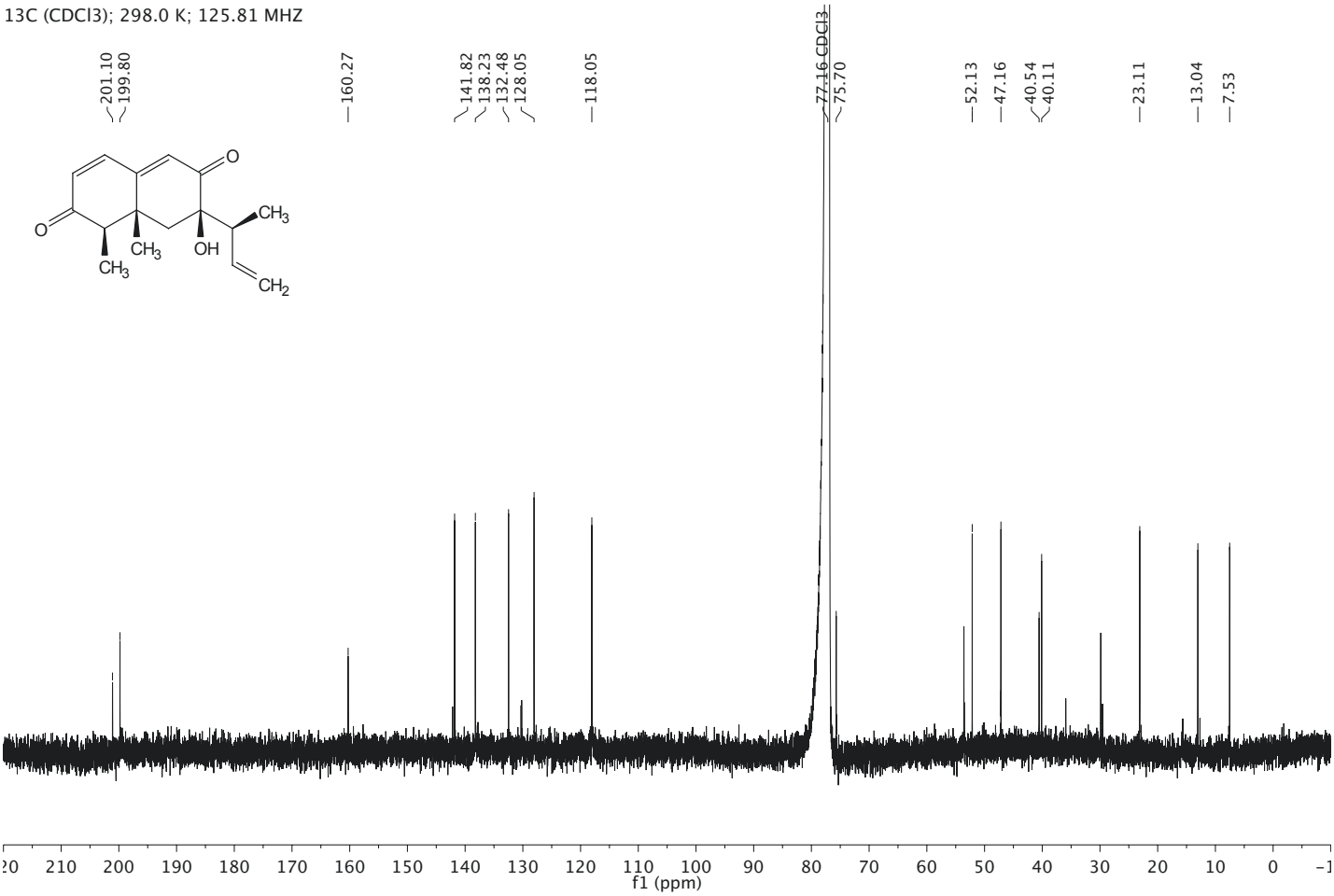
13C (CDCl3); 298.1 K; 100.62 MHZ



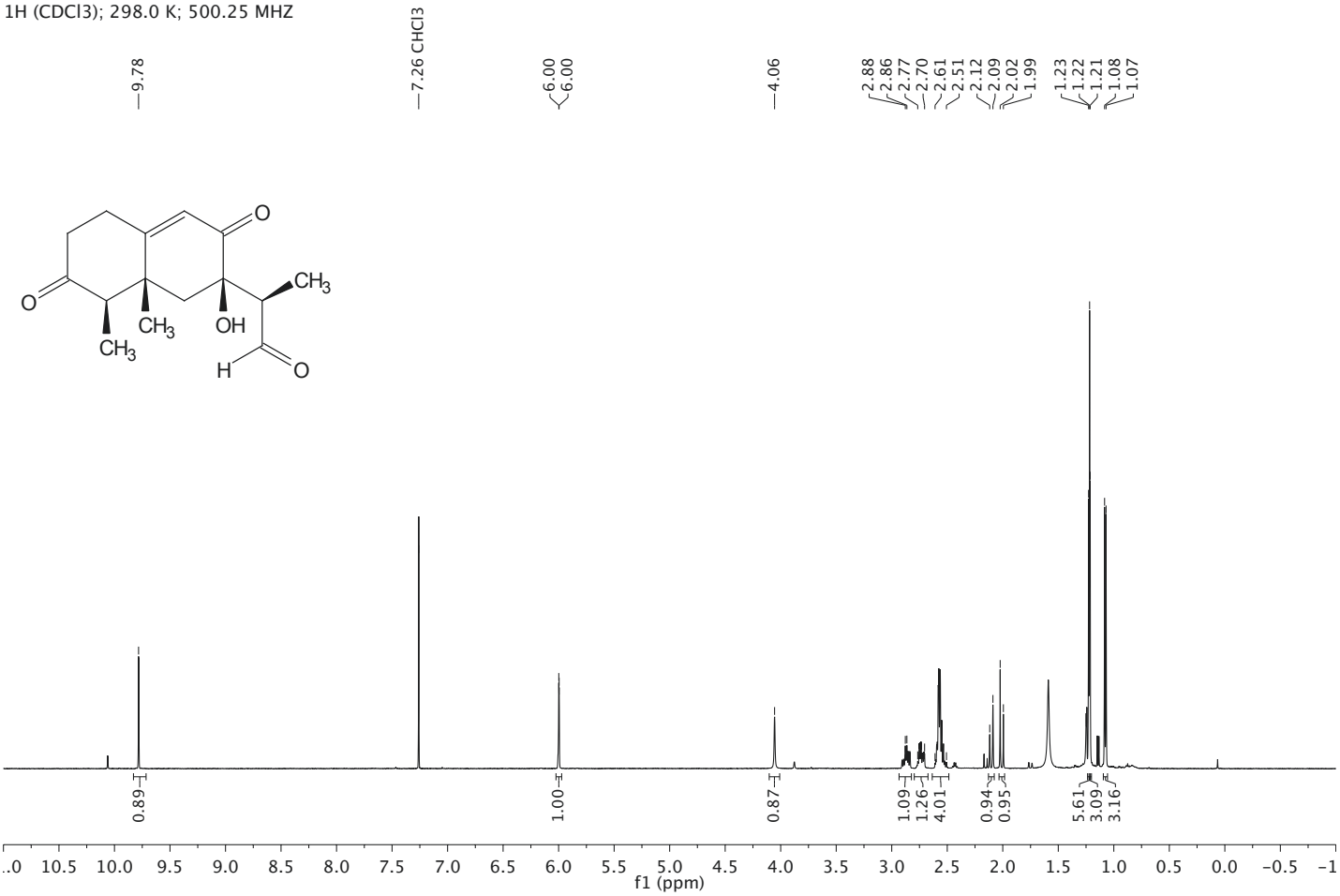
1H (CDCl3); 298.0 K; 400.23 MHZ



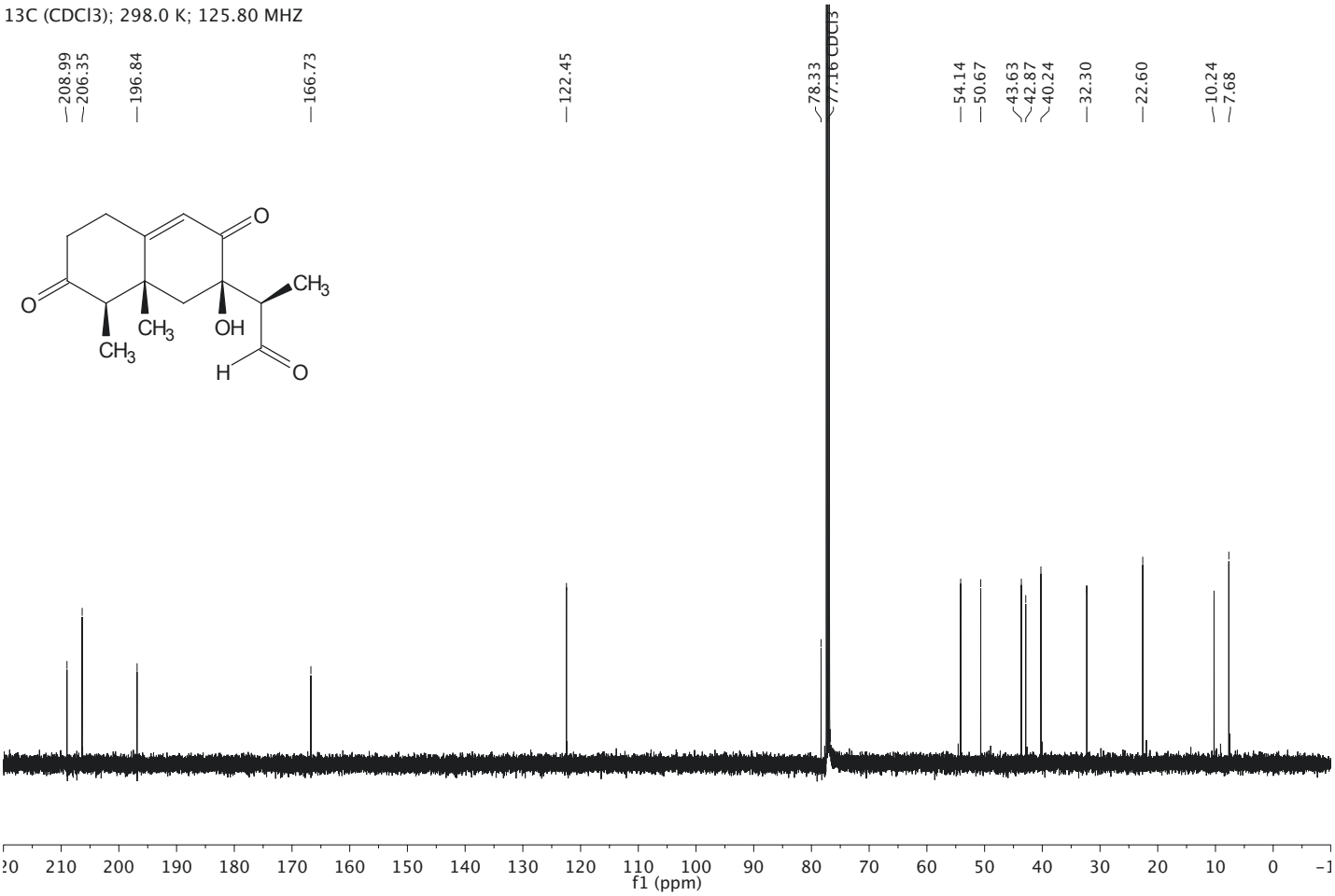
13C (CDCl3); 298.0 K; 125.81 MHZ



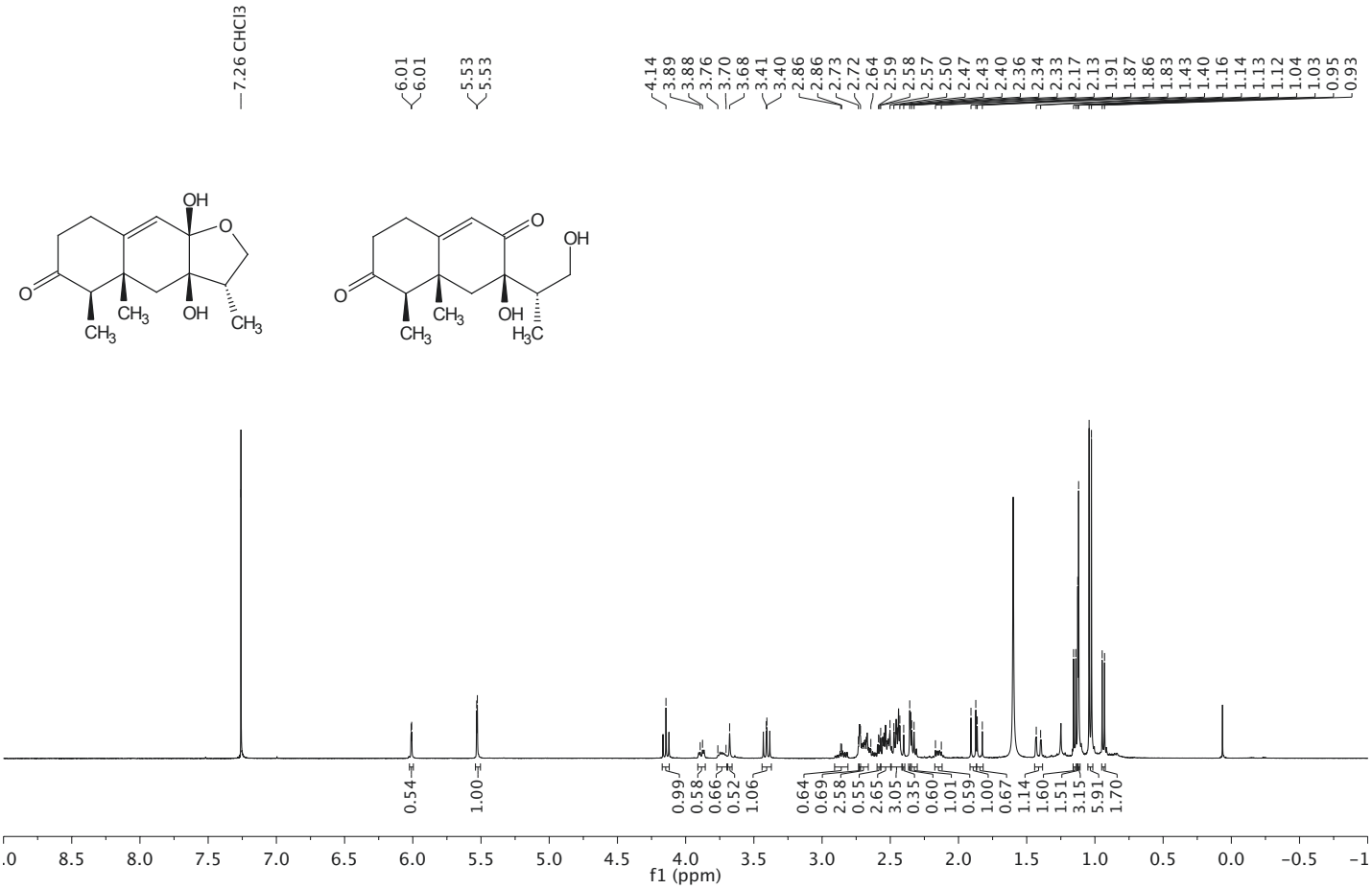
1H (CDCl3); 298.0 K; 500.25 MHZ



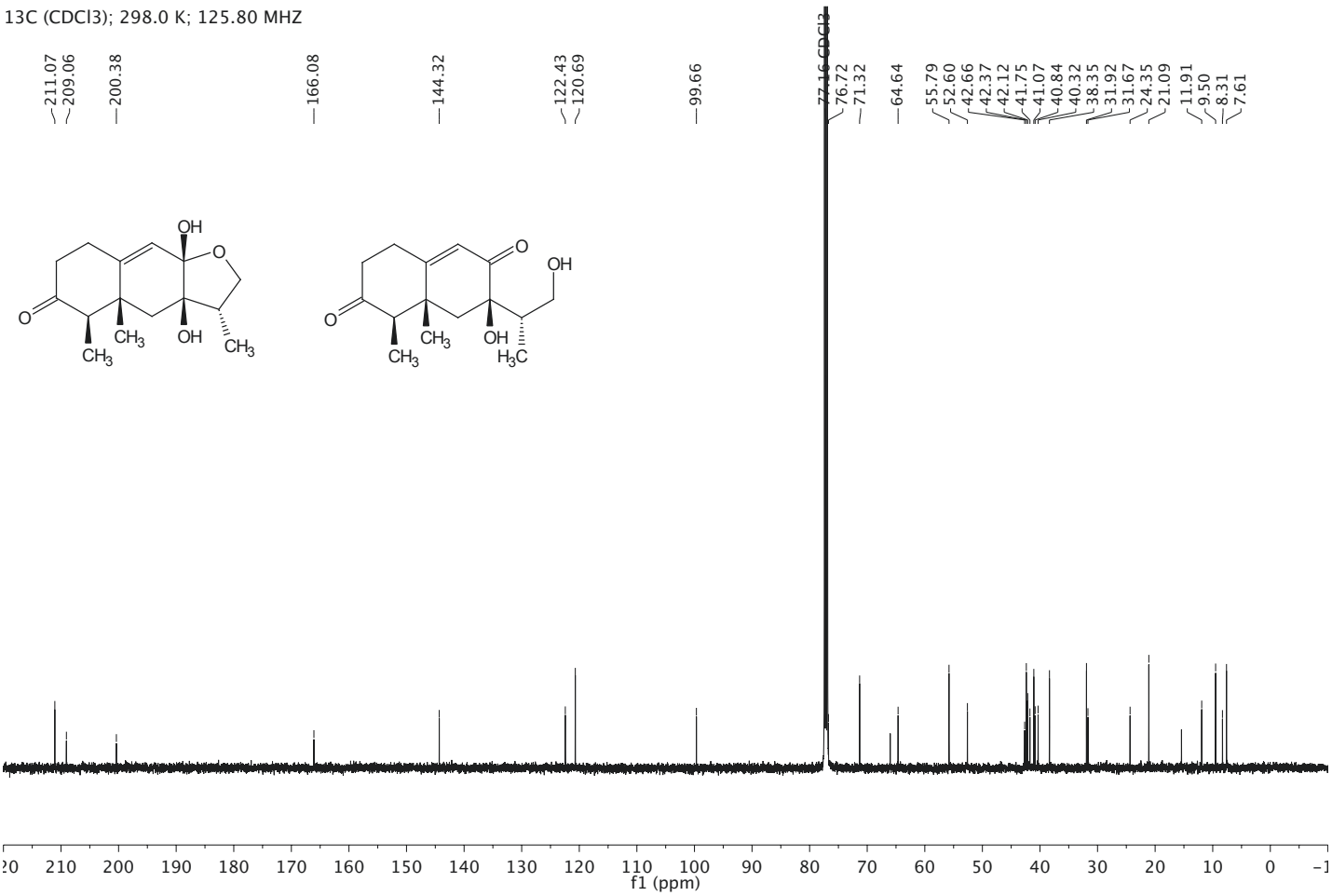
13C (CDCl3); 298.0 K; 125.80 MHZ



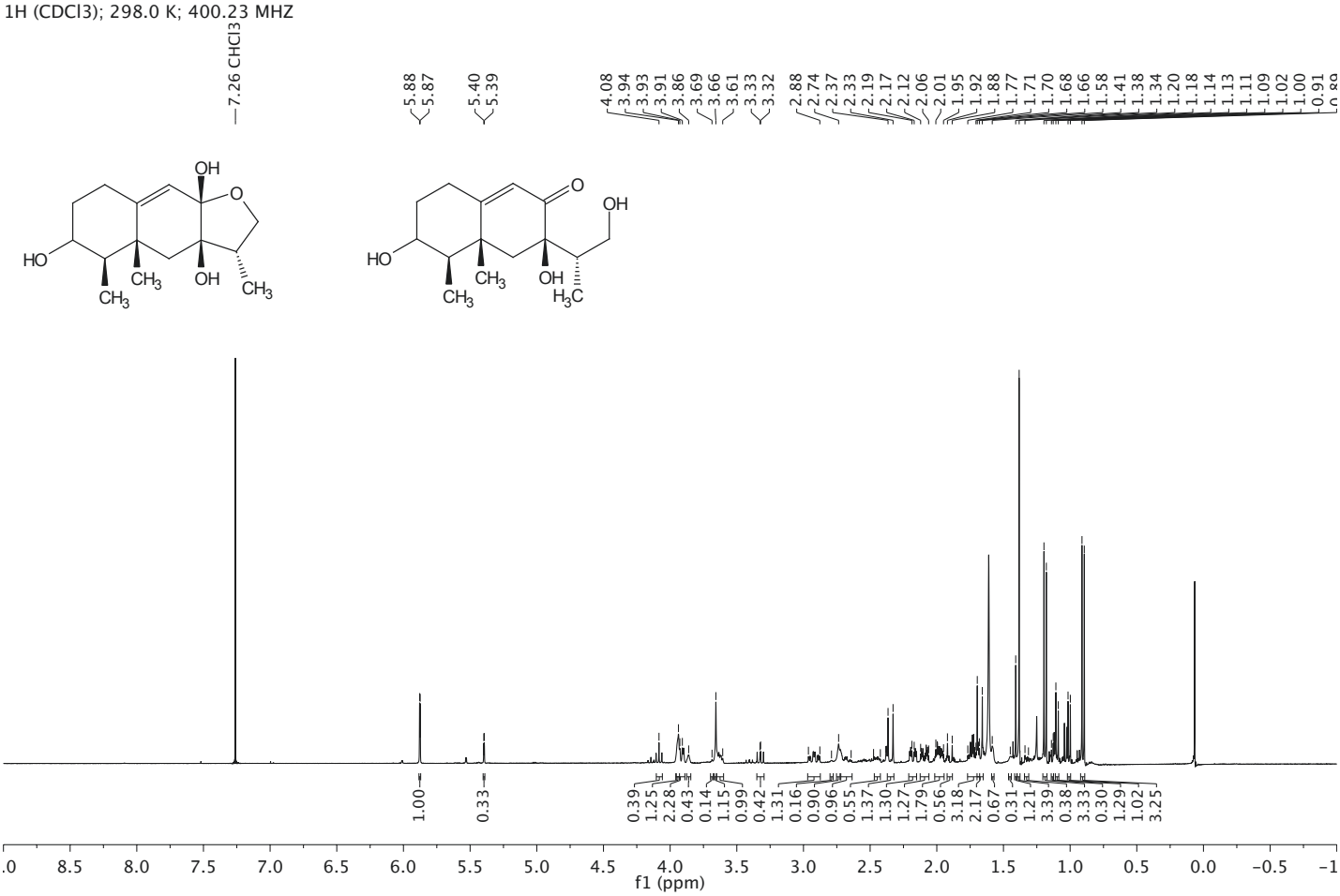
1H (CDCl3); 298.0 K; 400.23 MHZ



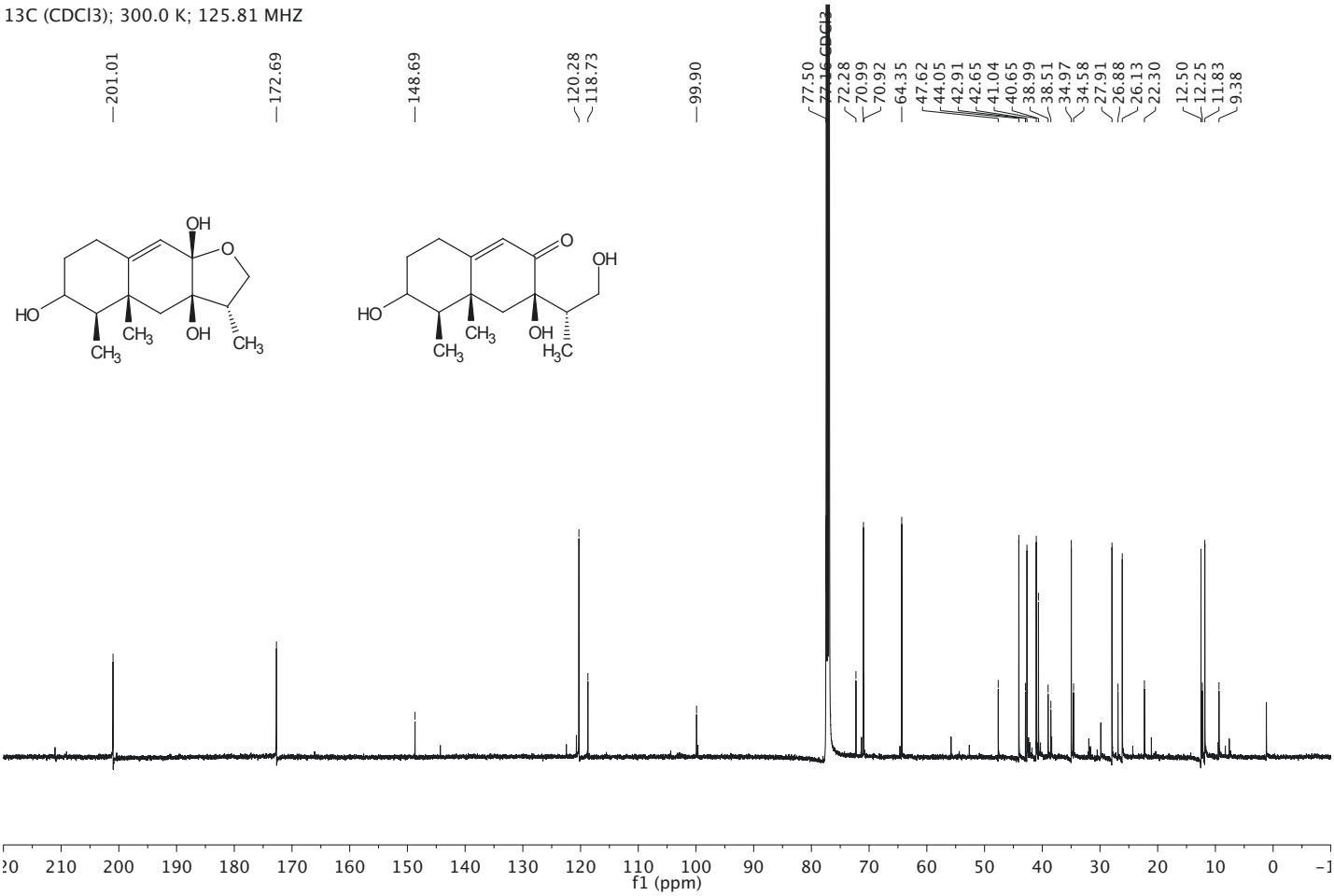
13C (CDCl3); 298.0 K; 125.80 MHZ

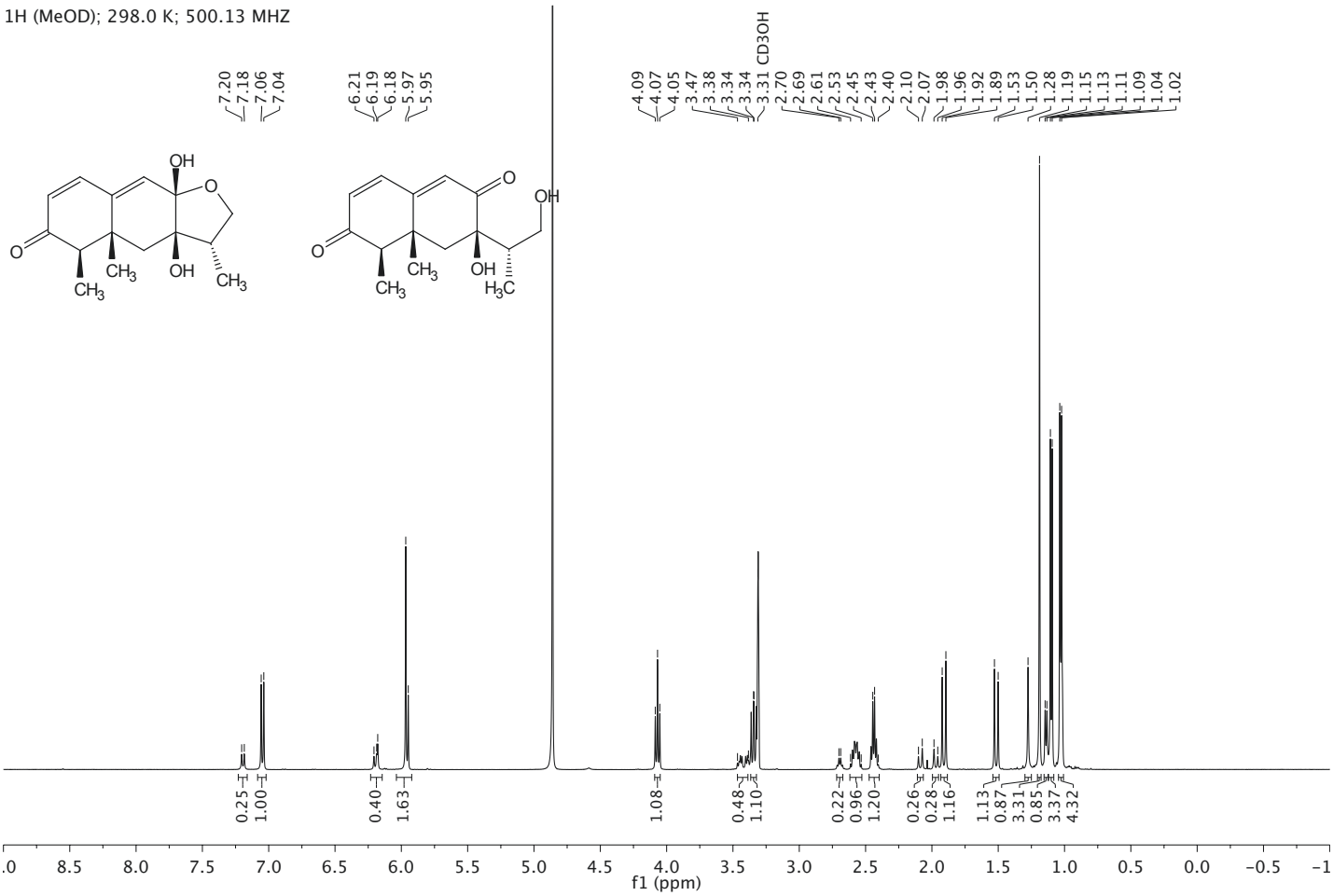


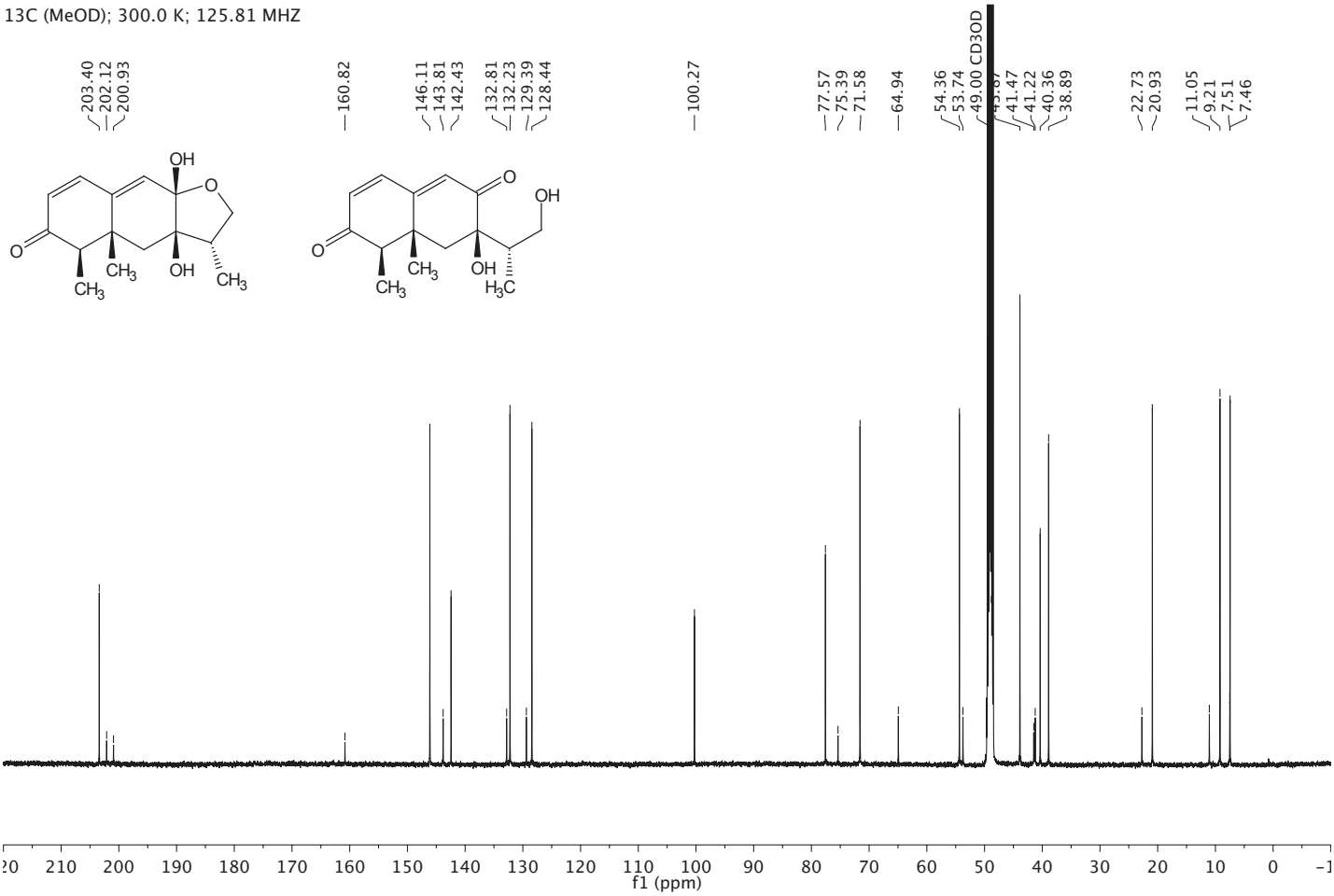
1H (CDCl3); 298.0 K; 400.23 MHZ



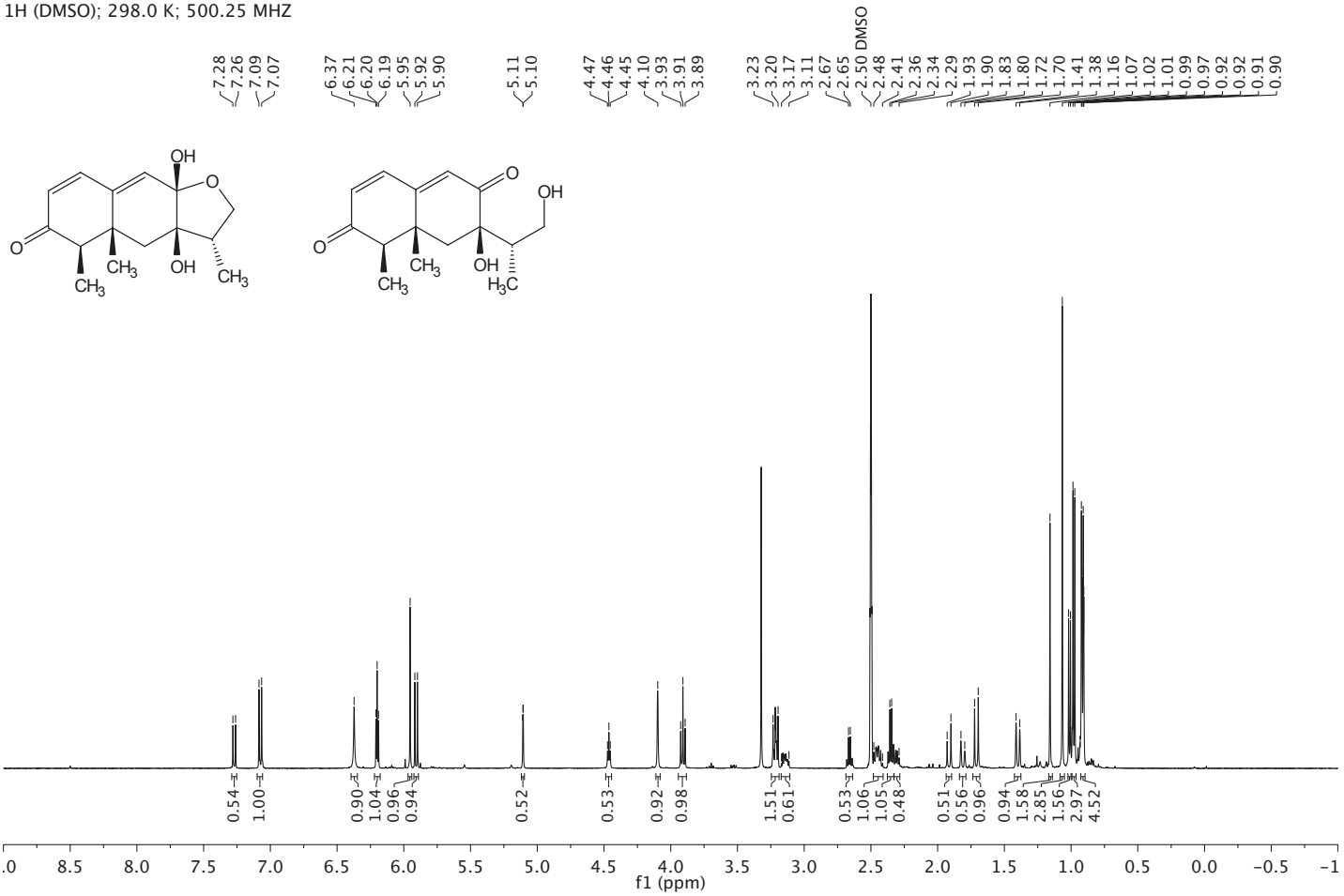
13C (CDCl3); 300.0 K; 125.81 MHZ



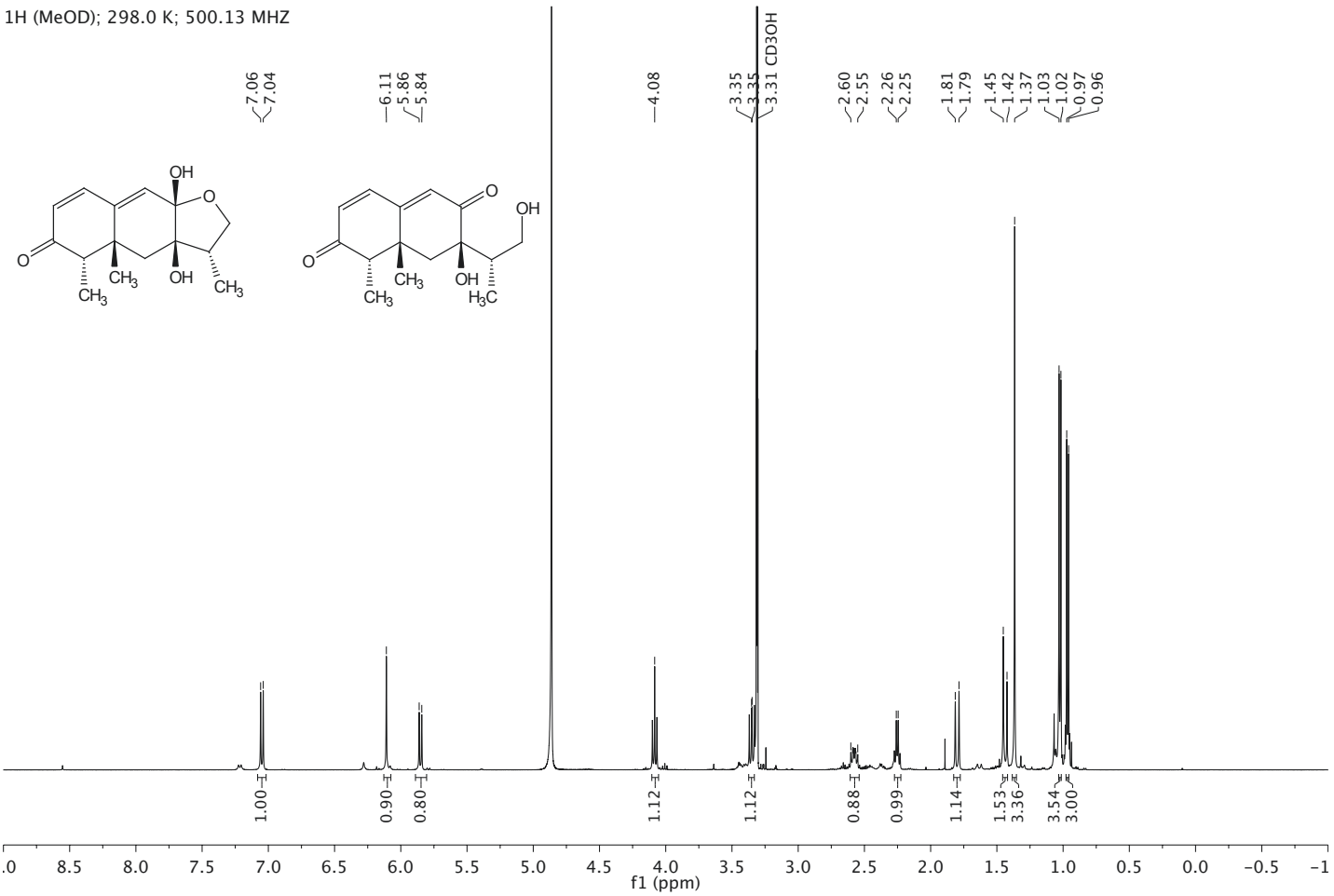

1H (MeOD); 298.0 K; 500.13 MHZ
7.20
7.18
7.06
7.04
6.21
6.19
6.18
5.97
5.95
4.09
4.07
4.05
3.47
3.38
3.34
3.34
3.31 CD3OH
2.70
2.69
2.61
2.53
2.45
2.43
2.40
2.10
2.07
1.98
1.96
1.92
1.89
1.53
1.50
1.28
1.19
1.15
1.13
1.11
1.09
1.04
1.02
OH
O
CH3
OH
CH3
CH3
OH
O
OH
CH3
OH
H3C
0.25
1.00
0.40
1.63
1.08
0.48
1.10
0.22
0.96
1.20
0.26
0.28
1.16
1.13
0.87
3.31
0.85
3.37
4.32
f1 (ppm)


13C (MeOD); 300.0 K; 125.81 MHZ
203.40
202.12
200.93
160.82
146.11
143.81
142.43
132.81
132.23
129.39
128.44
100.27
77.57
75.39
71.58
64.94
54.36
53.74
49.00 CD3OD
41.47
41.22
40.36
38.89
22.73
20.93
11.05
9.21
7.51
7.46
OH
O
CH3
OH
CH3
CH3
OH
O
OH
CH3
OH
H3C
f1 (ppm)

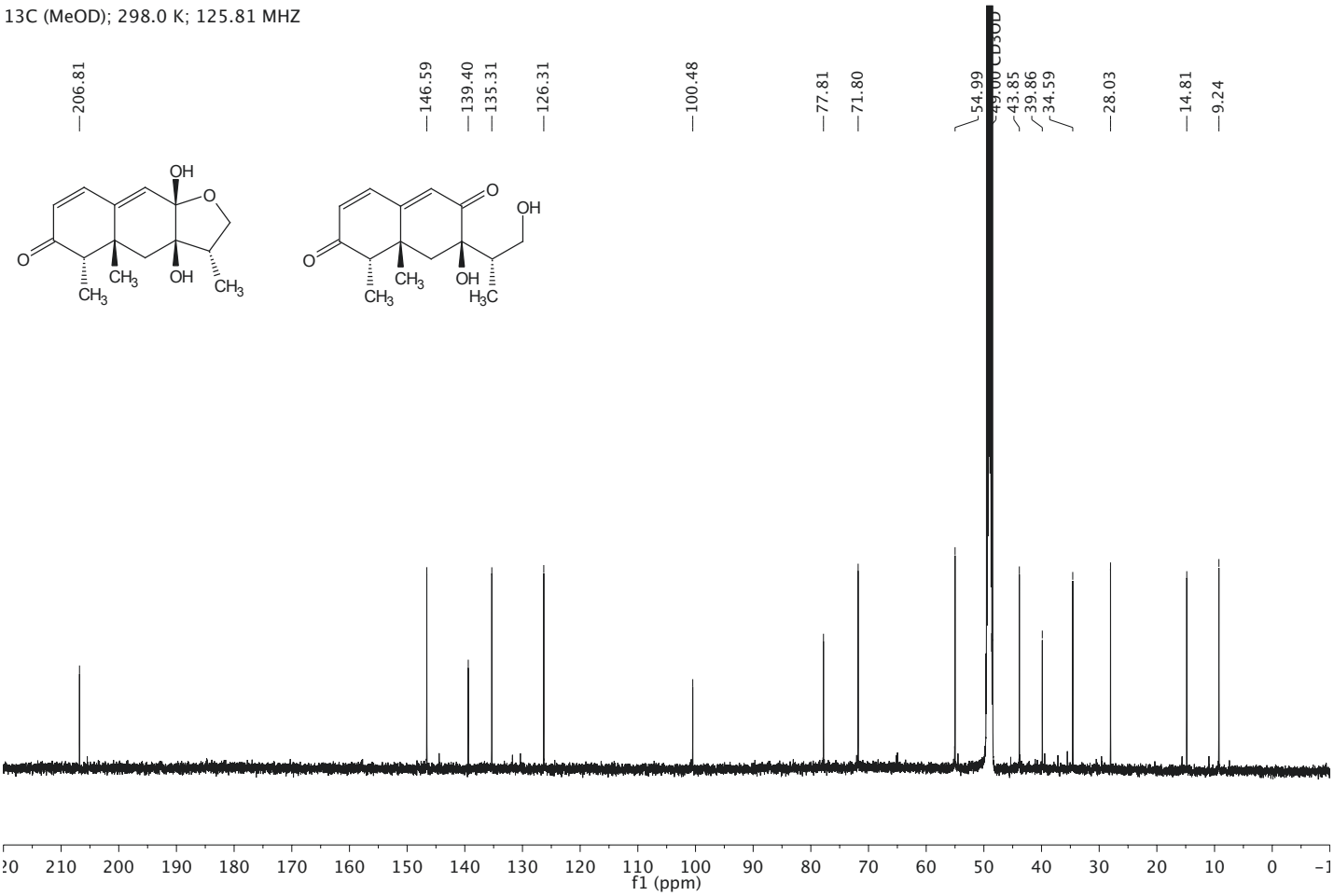
1H (DMSO); 298.0 K; 500.25 MHZ



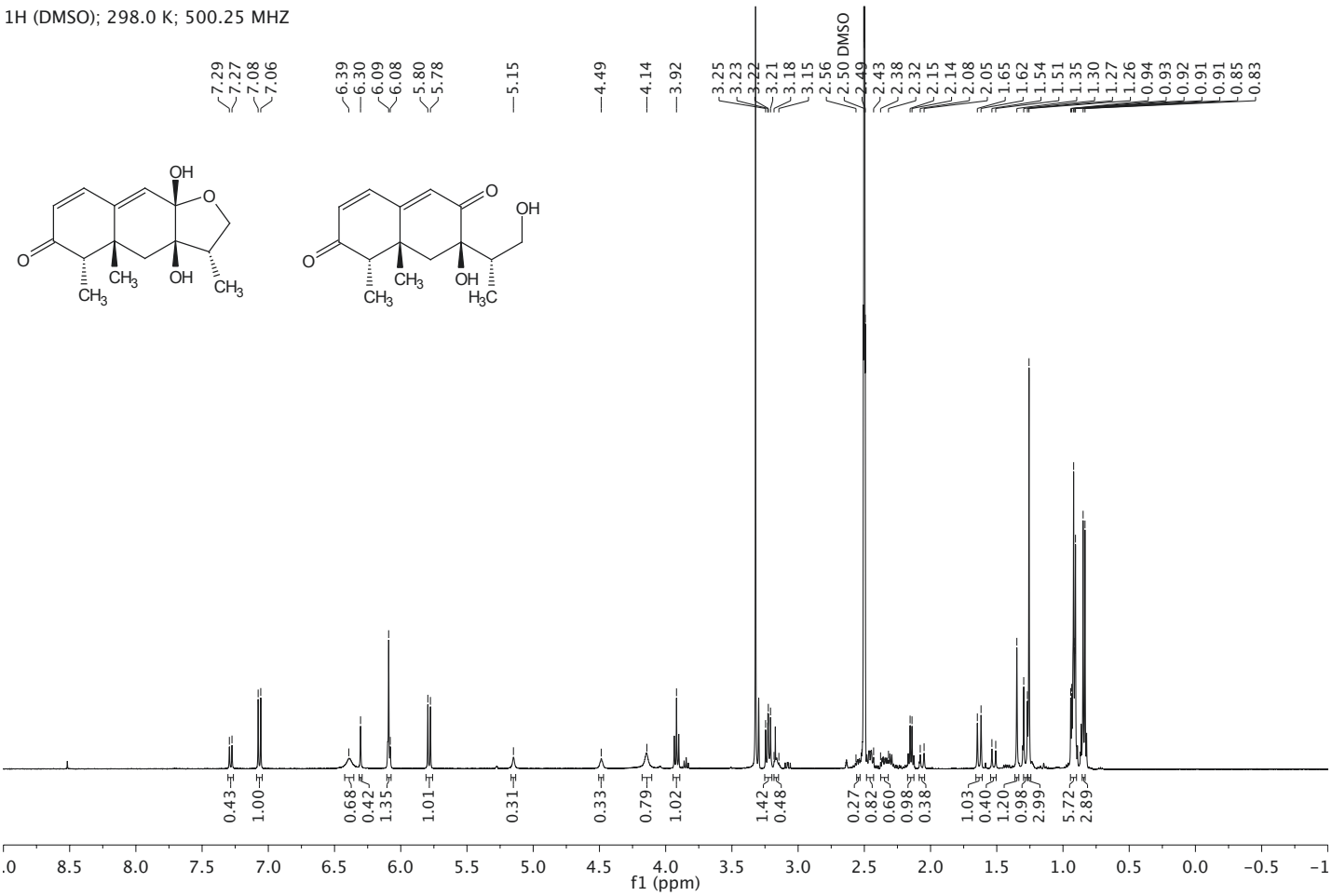
1H (MeOD); 298.0 K; 500.13 MHZ



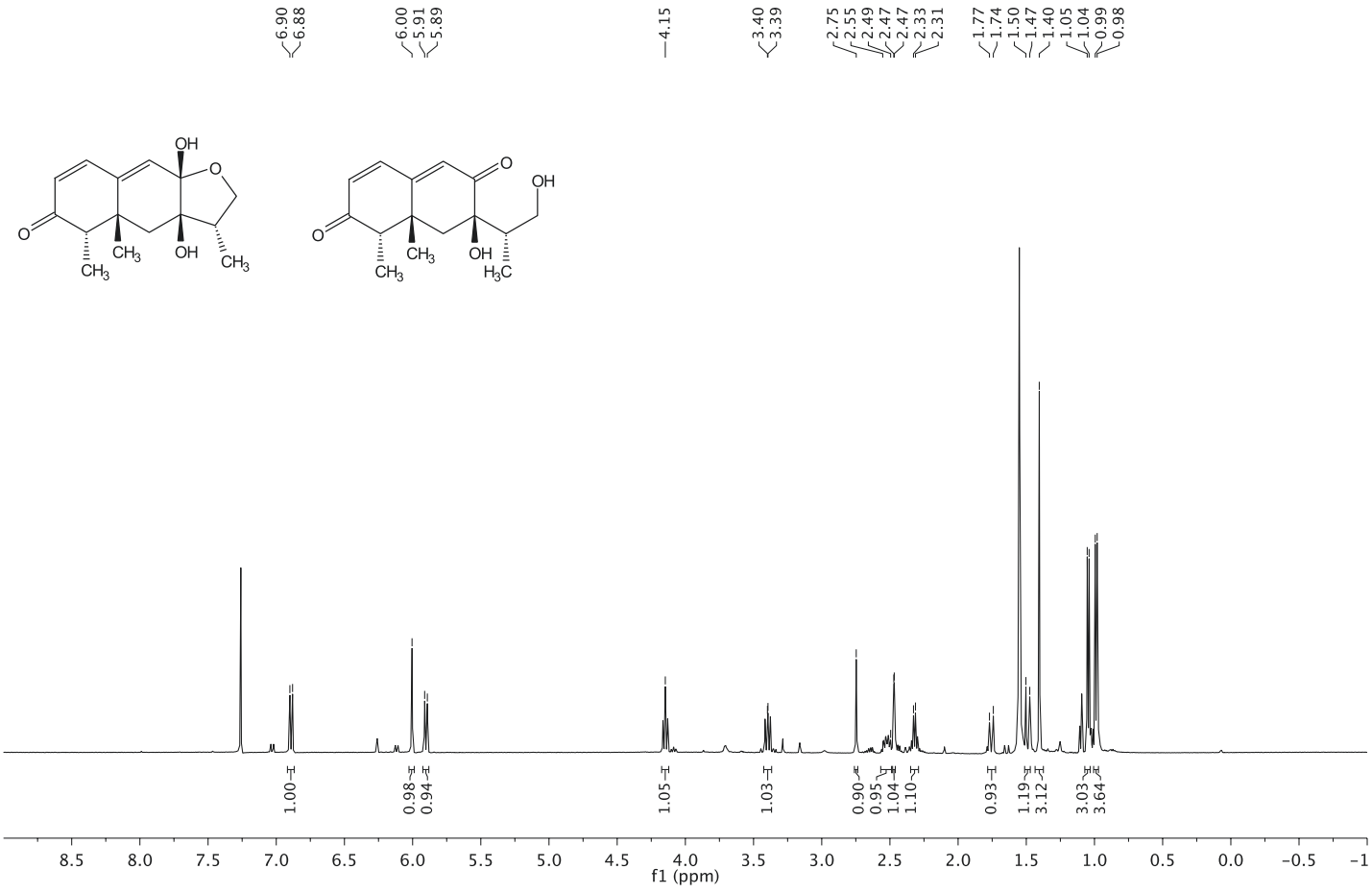
13C (MeOD); 298.0 K; 125.81 MHZ



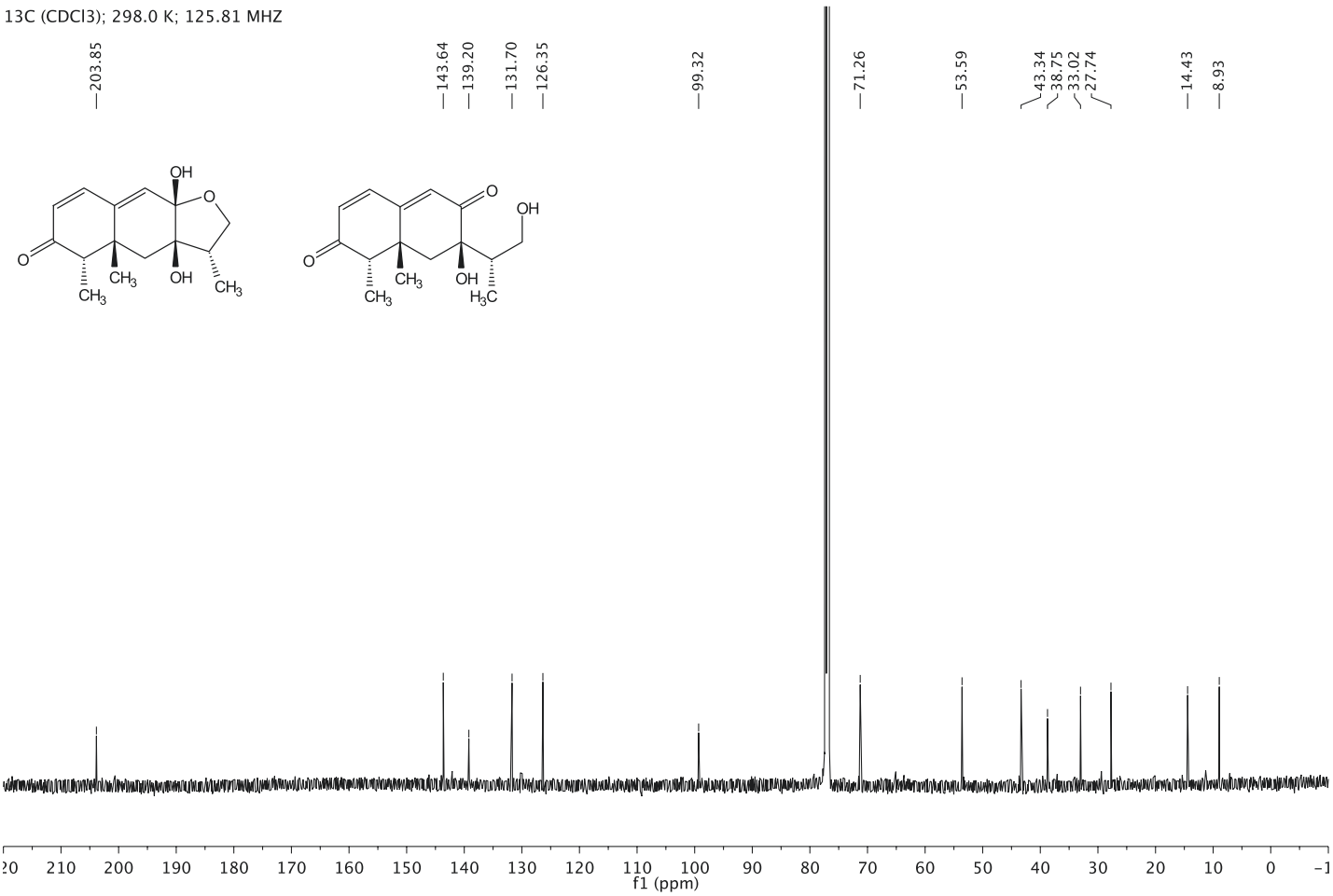
1H (DMSO); 298.0 K; 500.25 MHZ

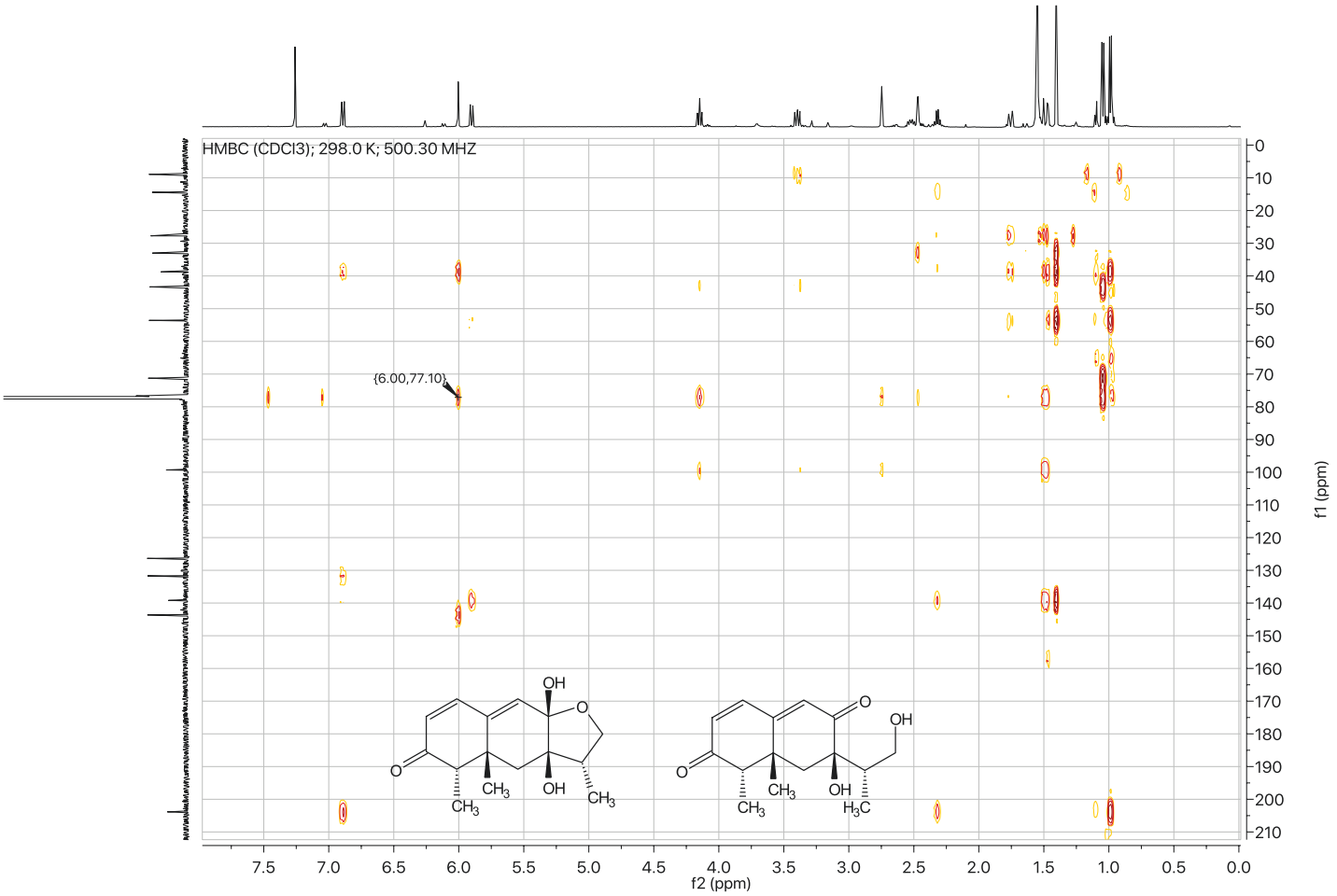


1H (CDCl3); 298.0 K; 500.30 MHZ

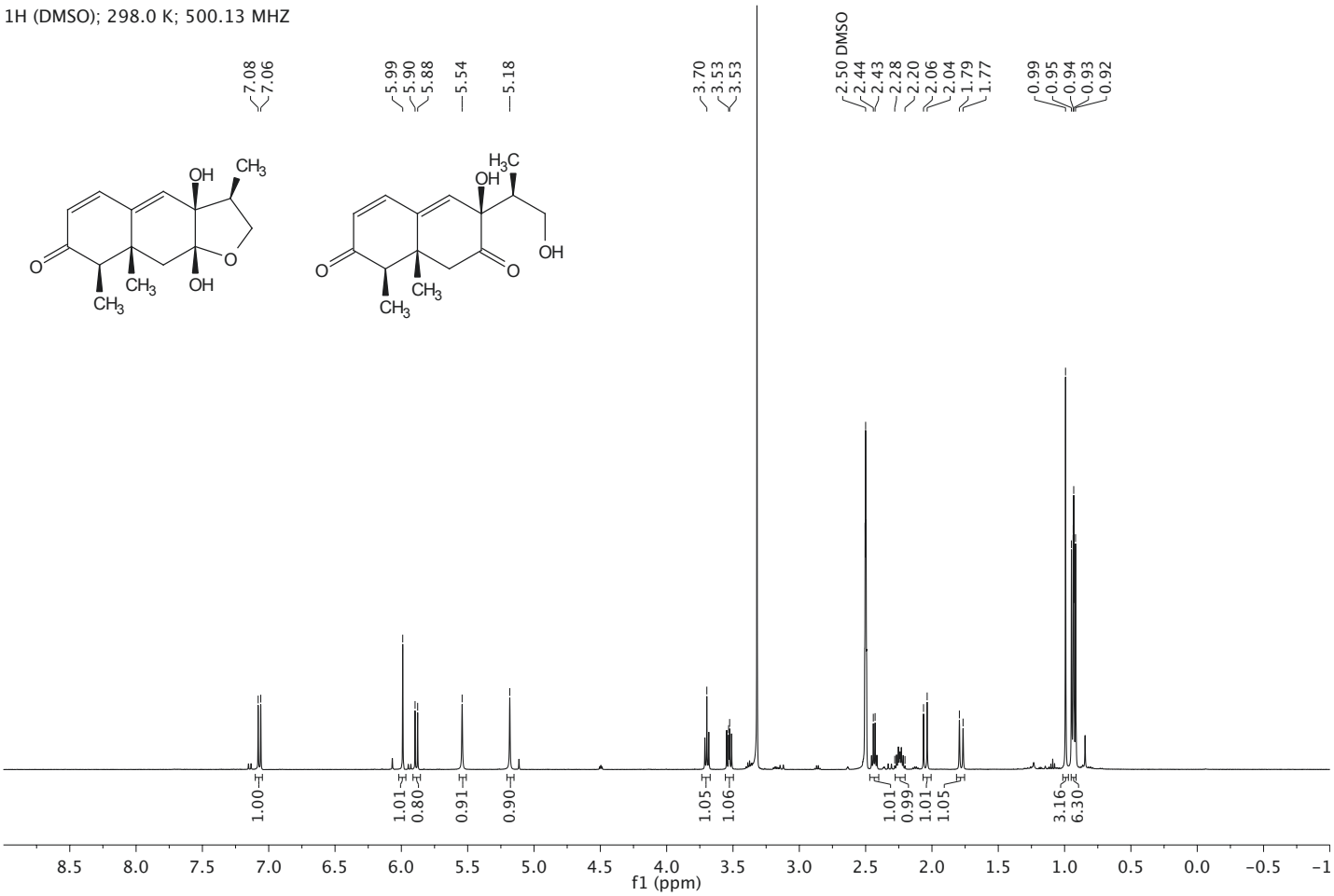


13C (CDCl3); 298.0 K; 125.81 MHZ

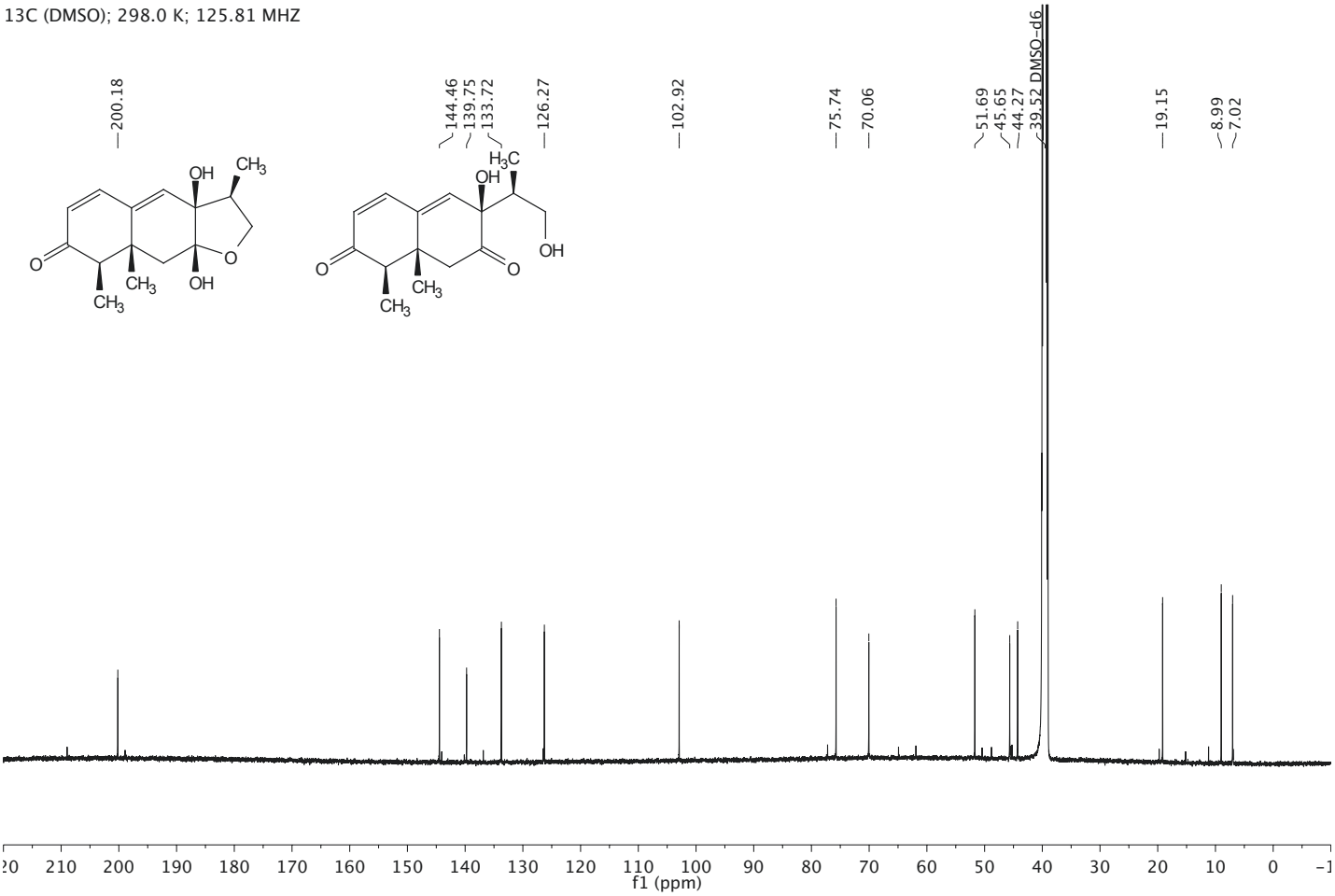



HMBC (CDCl3); 298.0 K; 500.30 MHZ
{6.00,77.10}
f2 (ppm)
f1 (ppm)
OH
O
CH3
OH
CH3
O
OH
CH3
OH
H3C

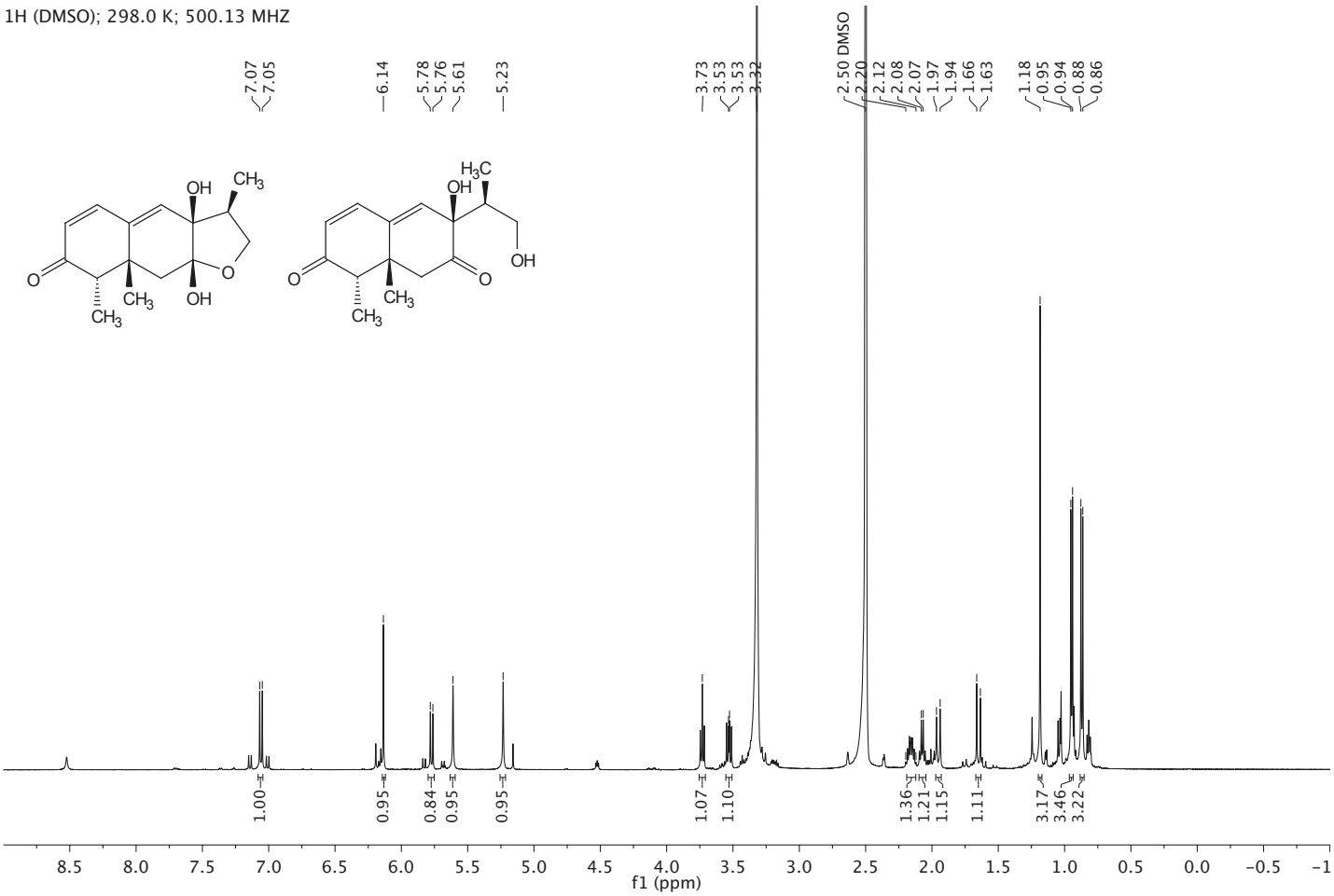
1H (DMSO); 298.0 K; 500.13 MHZ



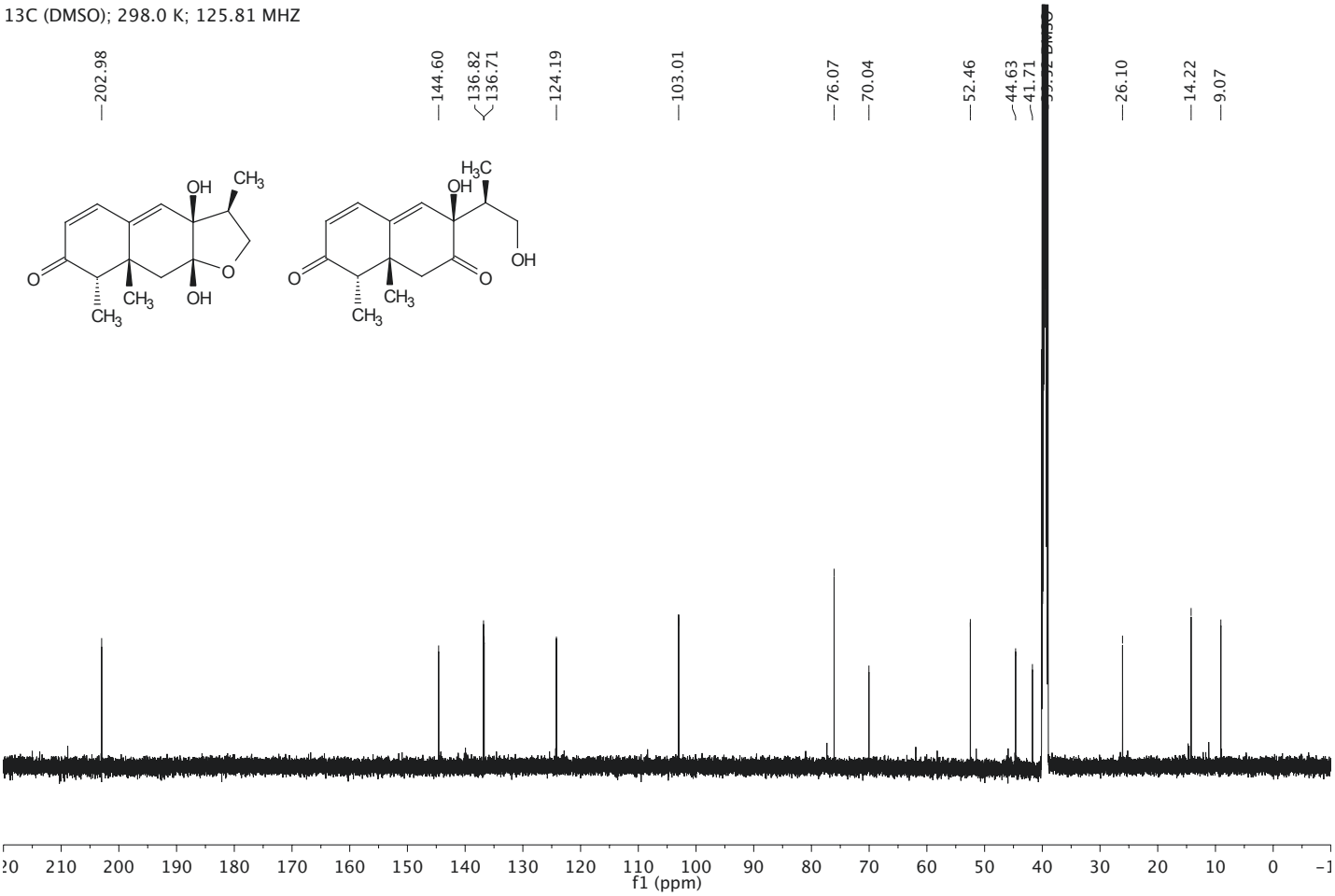
13C (DMSO); 298.0 K; 125.81 MHZ



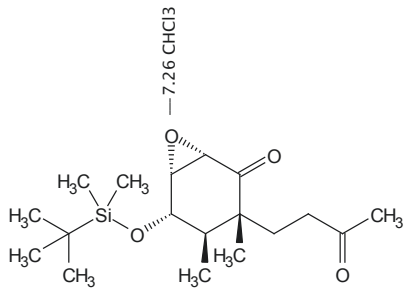
1H (DMSO); 298.0 K; 500.13 MHZ



13C (DMSO); 298.0 K; 125.81 MHZ



1H (CDCl3); 298.9 K; 500.13 MHZ



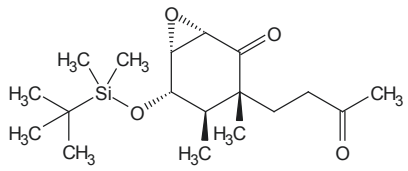
7.26 CHCl3

3.91 3.89 3.50 3.49 3.32 3.31 2.37 2.31 2.24 2.14 2.11 2.11 2.08 2.03 1.97 1.68 1.62 1.60 0.95 0.94 0.94 0.92 0.91 0.90 0.16 0.13

1.01 1.03 0.93 1.11 1.10 4.16 1.12 1.19 9.50 3.27 3.61 3.04 3.11

f1 (ppm)

13C (CDCl3); 300.0 K; 150.94 MHZ



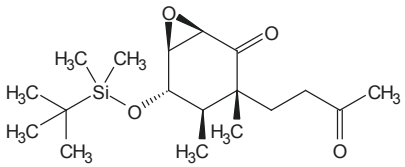
208.13 208.09

77.16 CDCl3

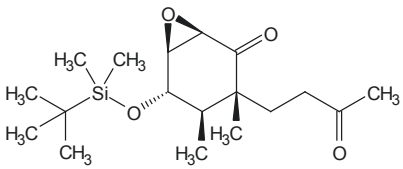
70.62 57.73 55.49 48.95 38.60 32.93 30.13 29.86 25.93 20.21 18.25 10.93 -3.91 -4.47

f1 (ppm)

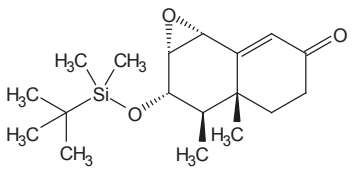
1H (CDCl3); 300.0 K; 400.13 MHZ



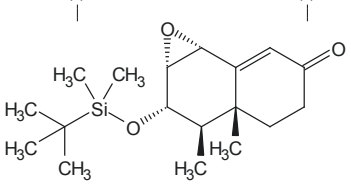
13C (CDCl3); 299.9 K; 150.94 MHZ



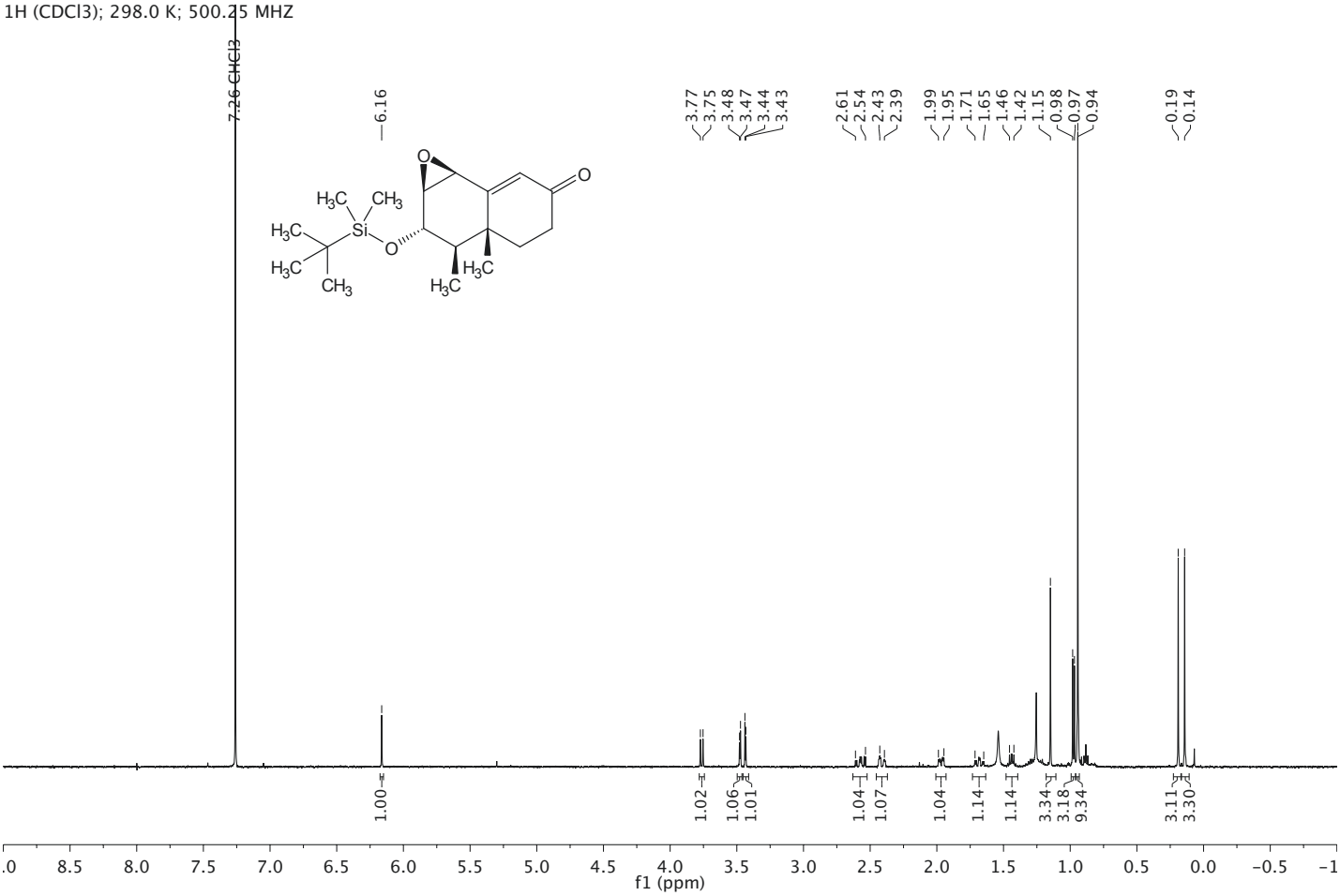
1H (CDCl3); 300.0 K; 500.13 MHZ



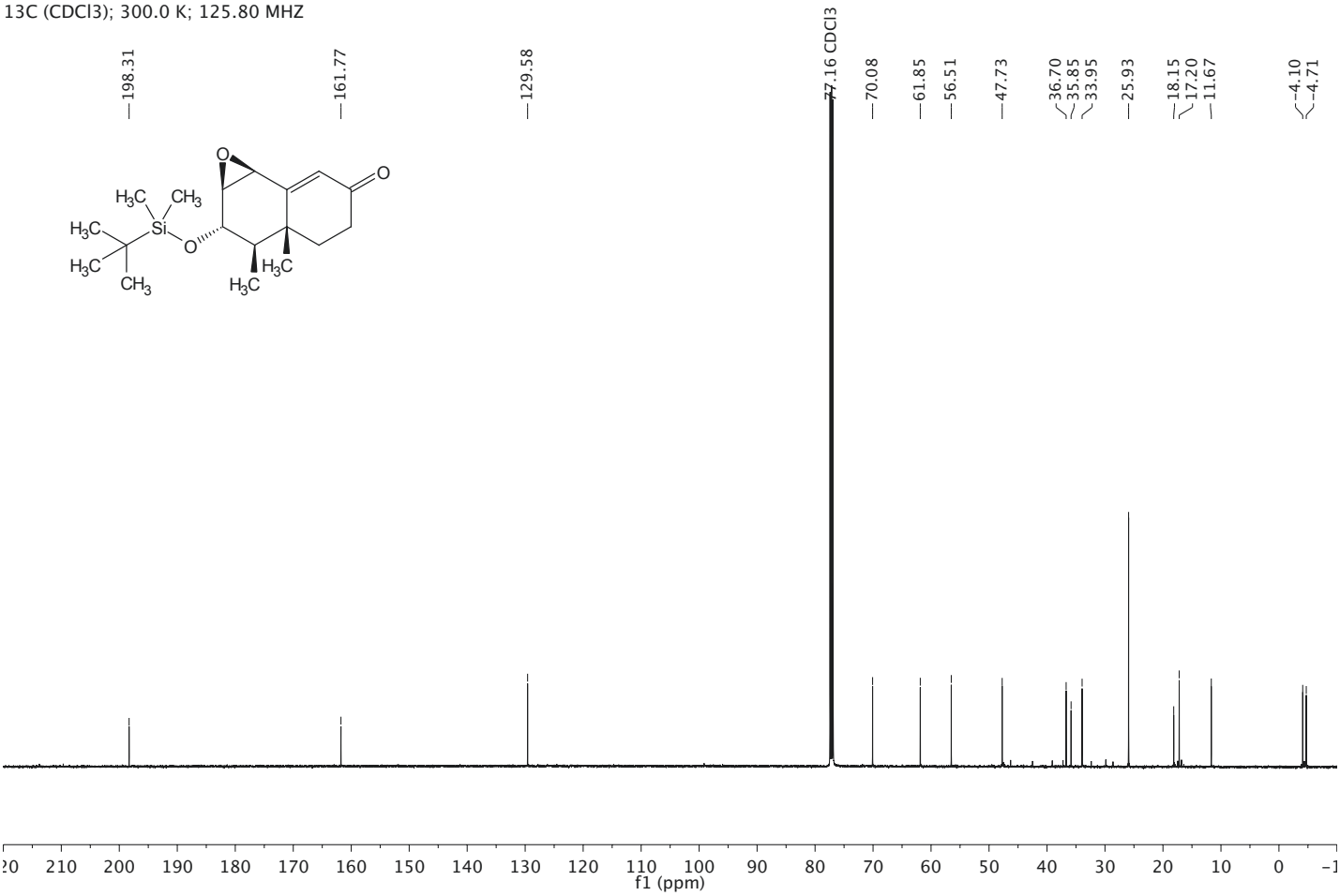
13C (CDCl3); 298.0 K; 125.80 MHZ



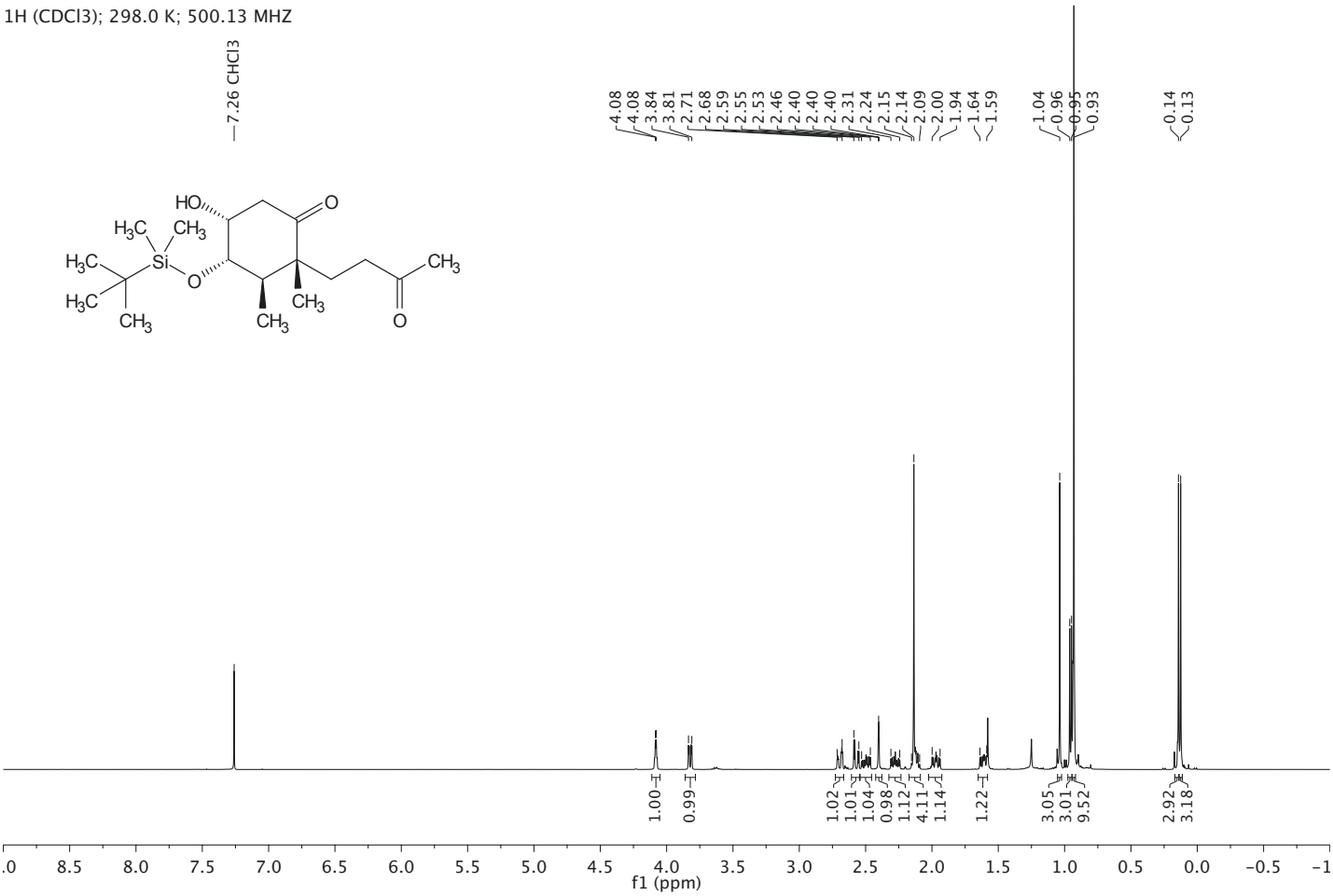
1H (CDCl3); 298.0 K; 500.25 MHZ



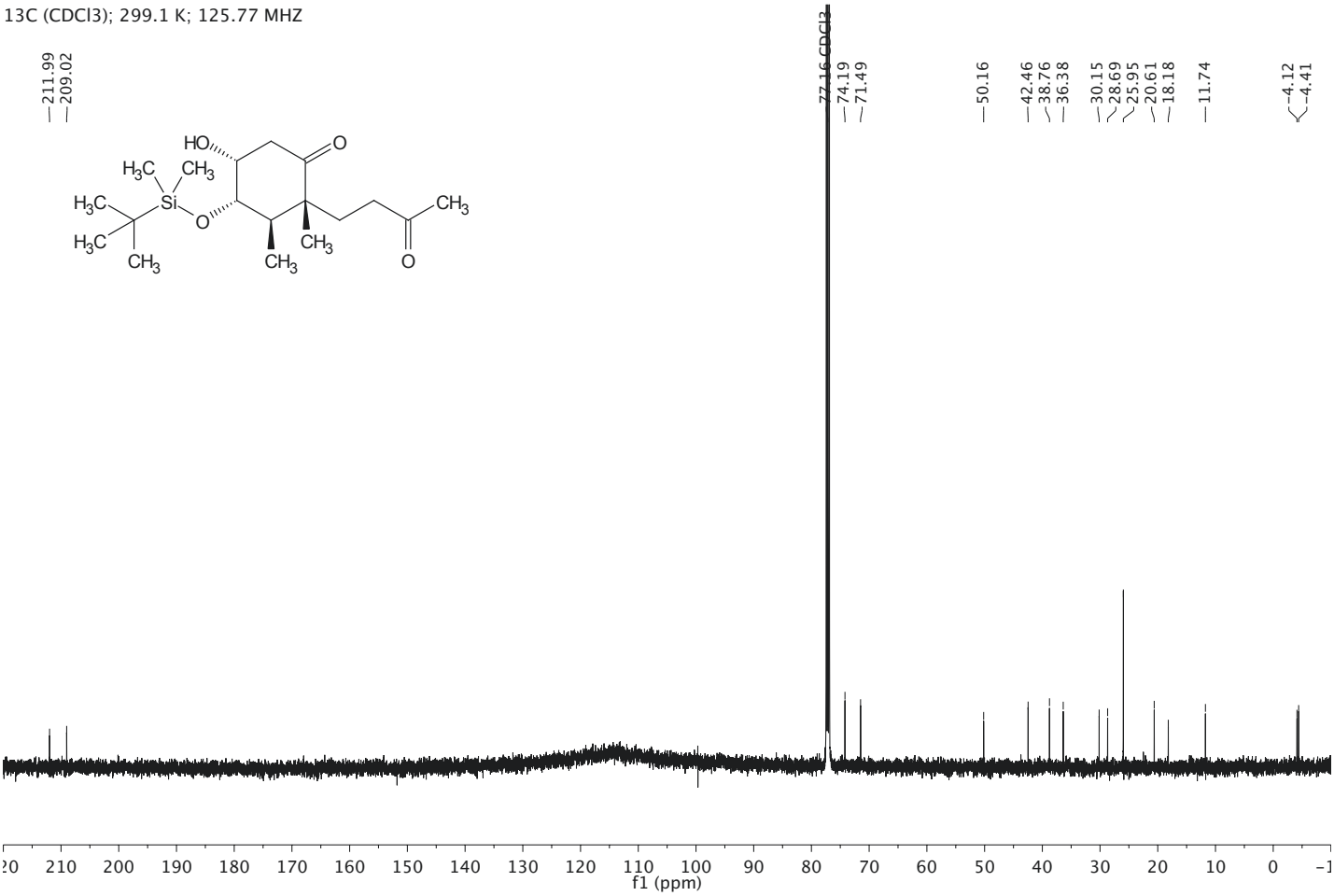
13C (CDCl3); 300.0 K; 125.80 MHZ



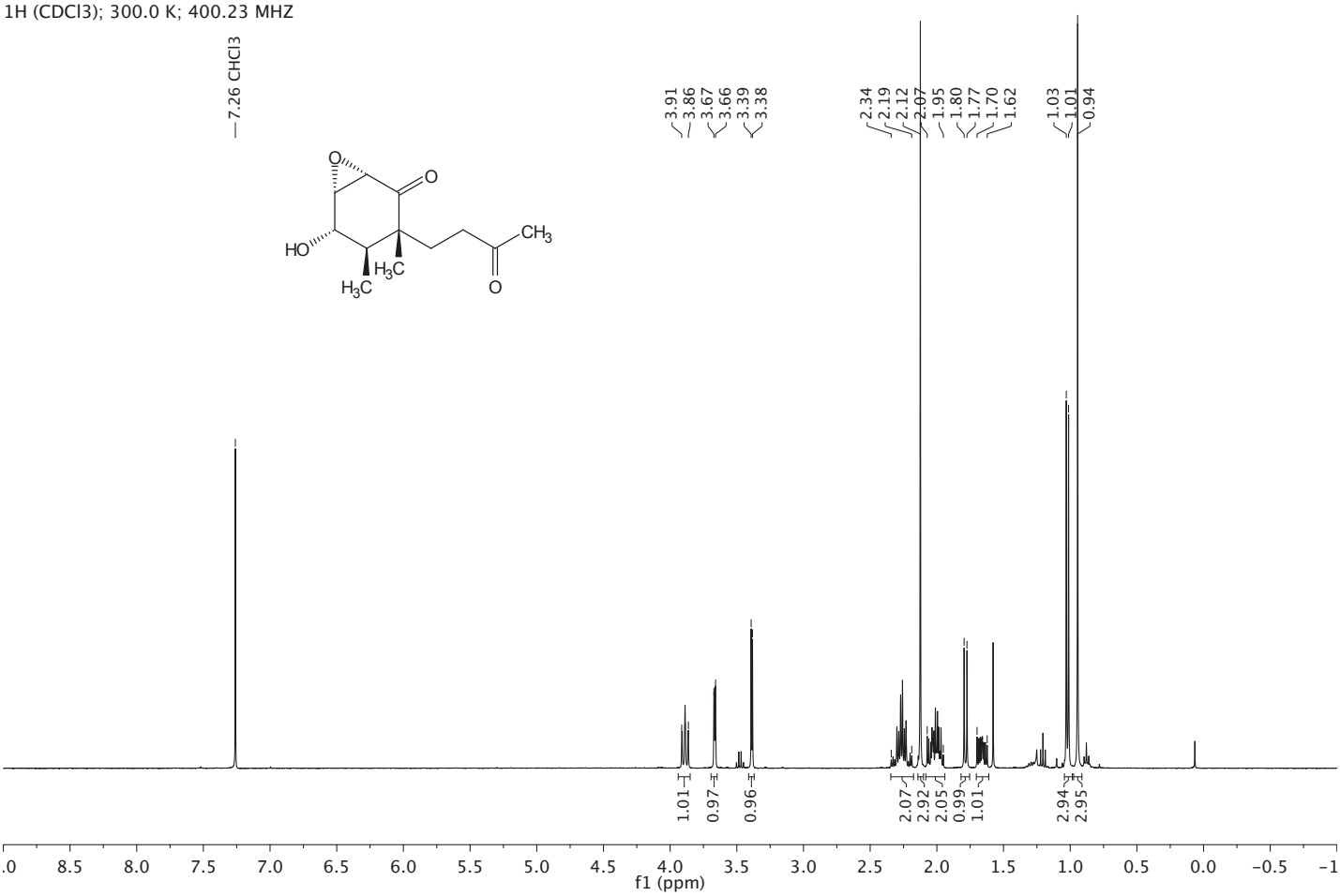
1H (CDCl3); 298.0 K; 500.13 MHZ



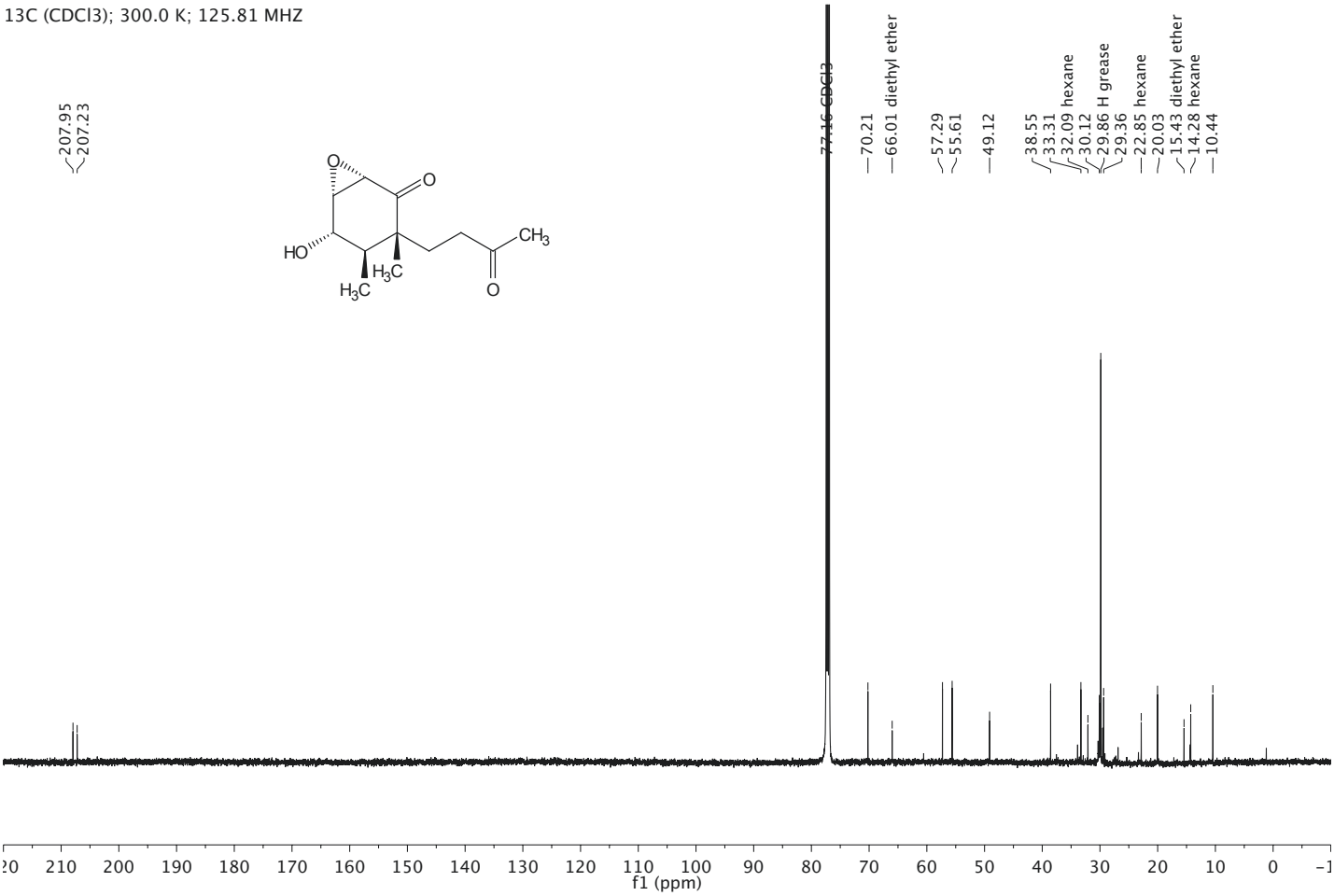
13C (CDCl3); 299.1 K; 125.77 MHZ



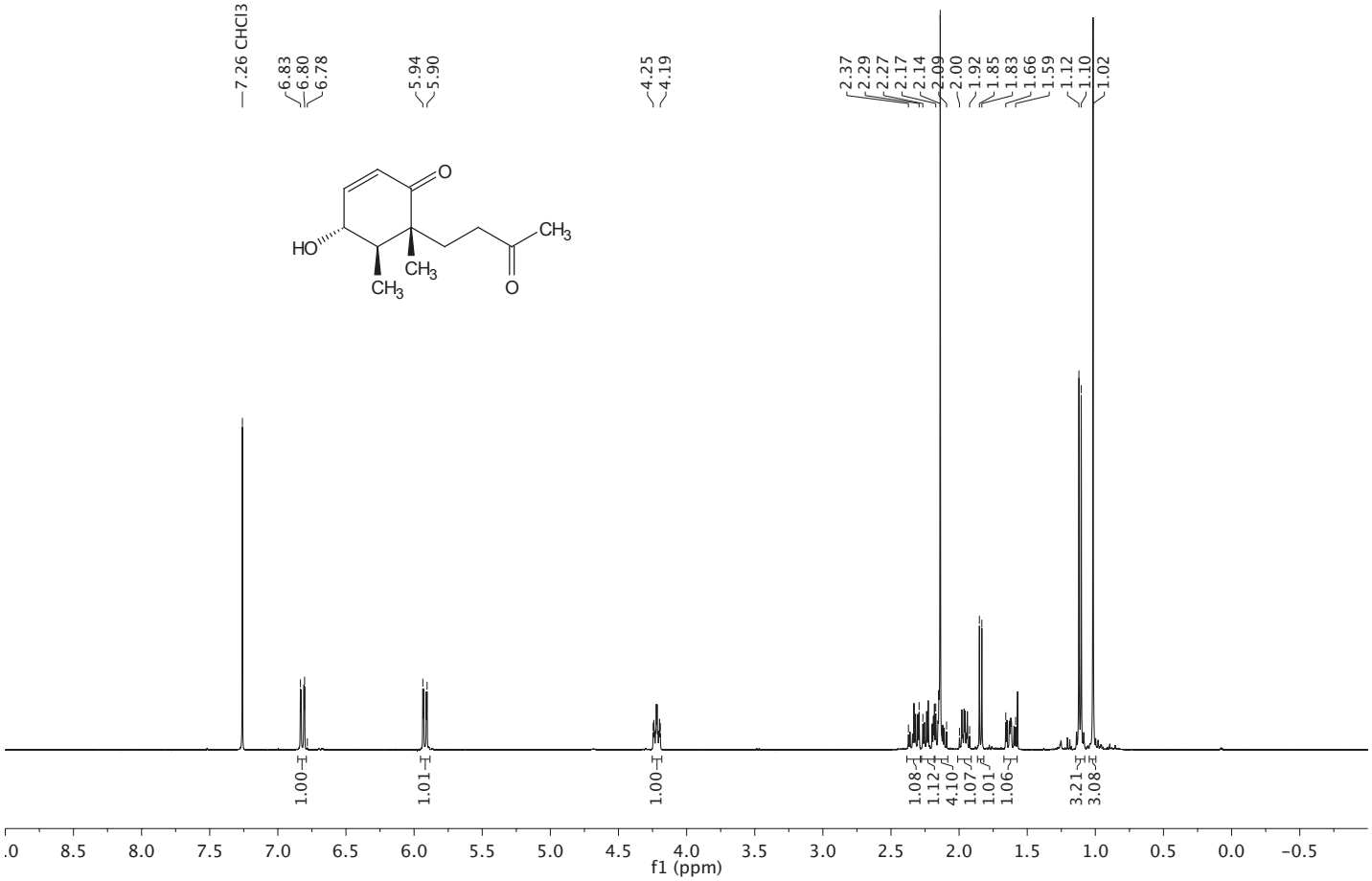
1H (CDCl3); 300.0 K; 400.23 MHZ



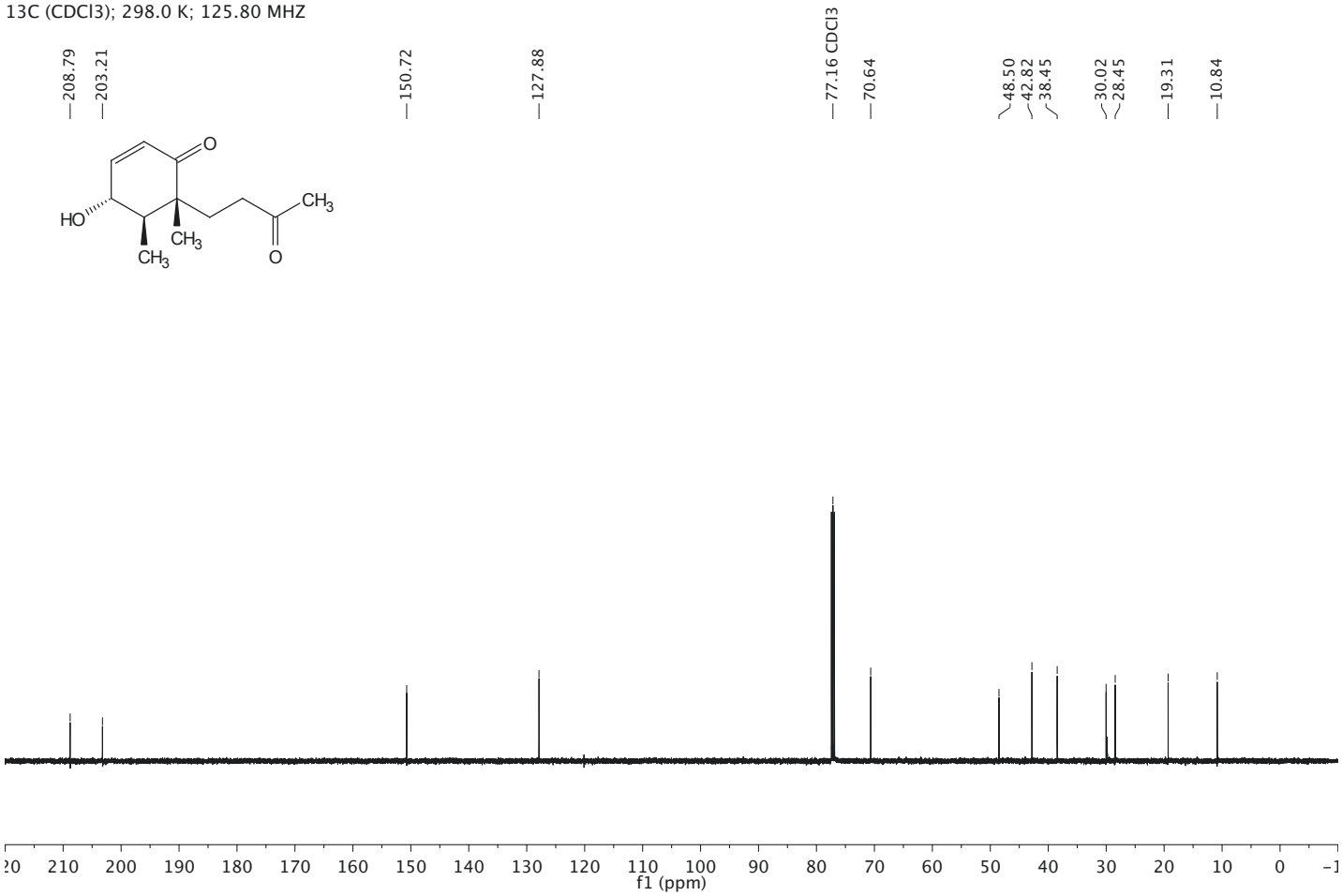
13C (CDCl3); 300.0 K; 125.81 MHZ



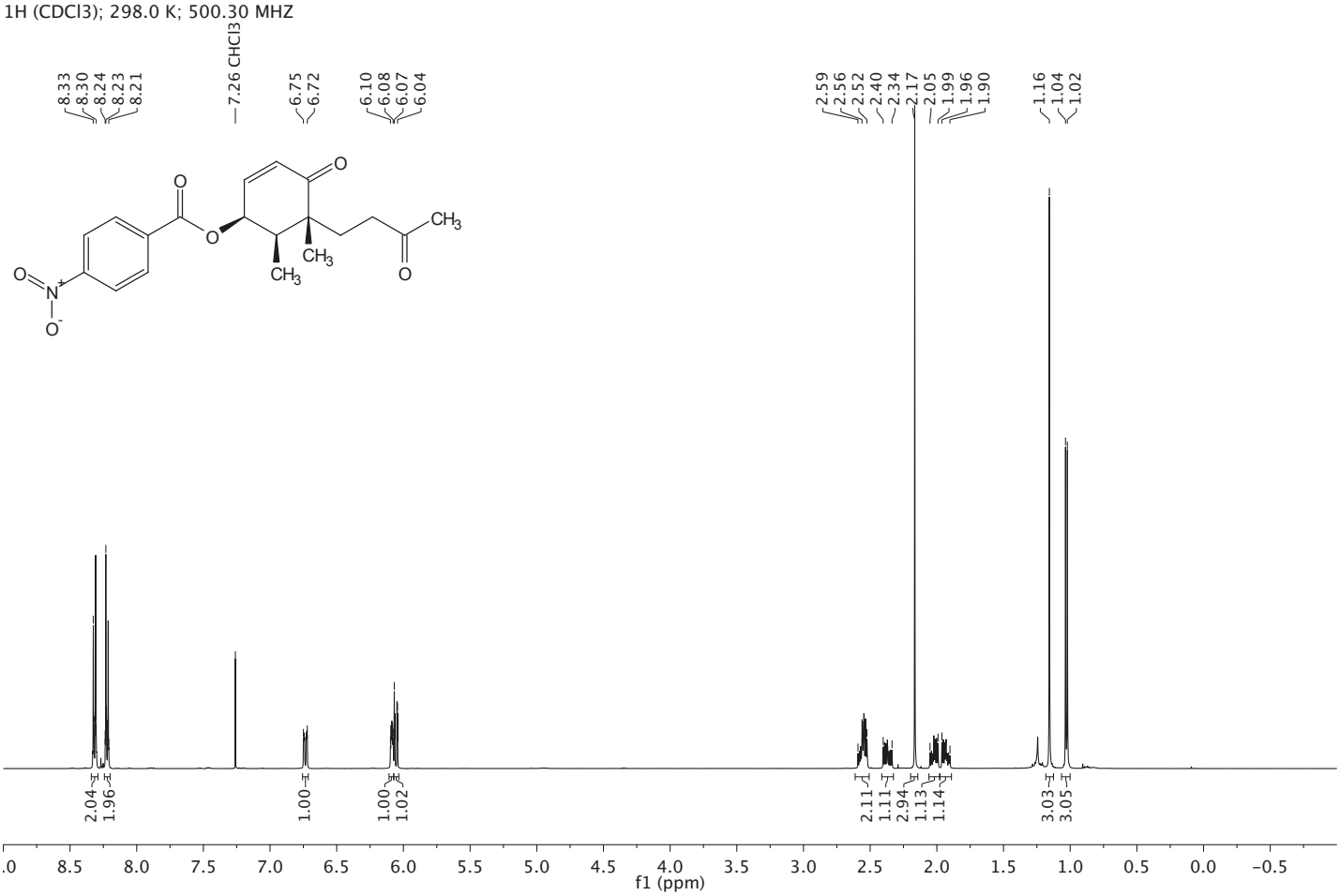
1H (CDCl3); 300.0 K; 400.13 MHZ



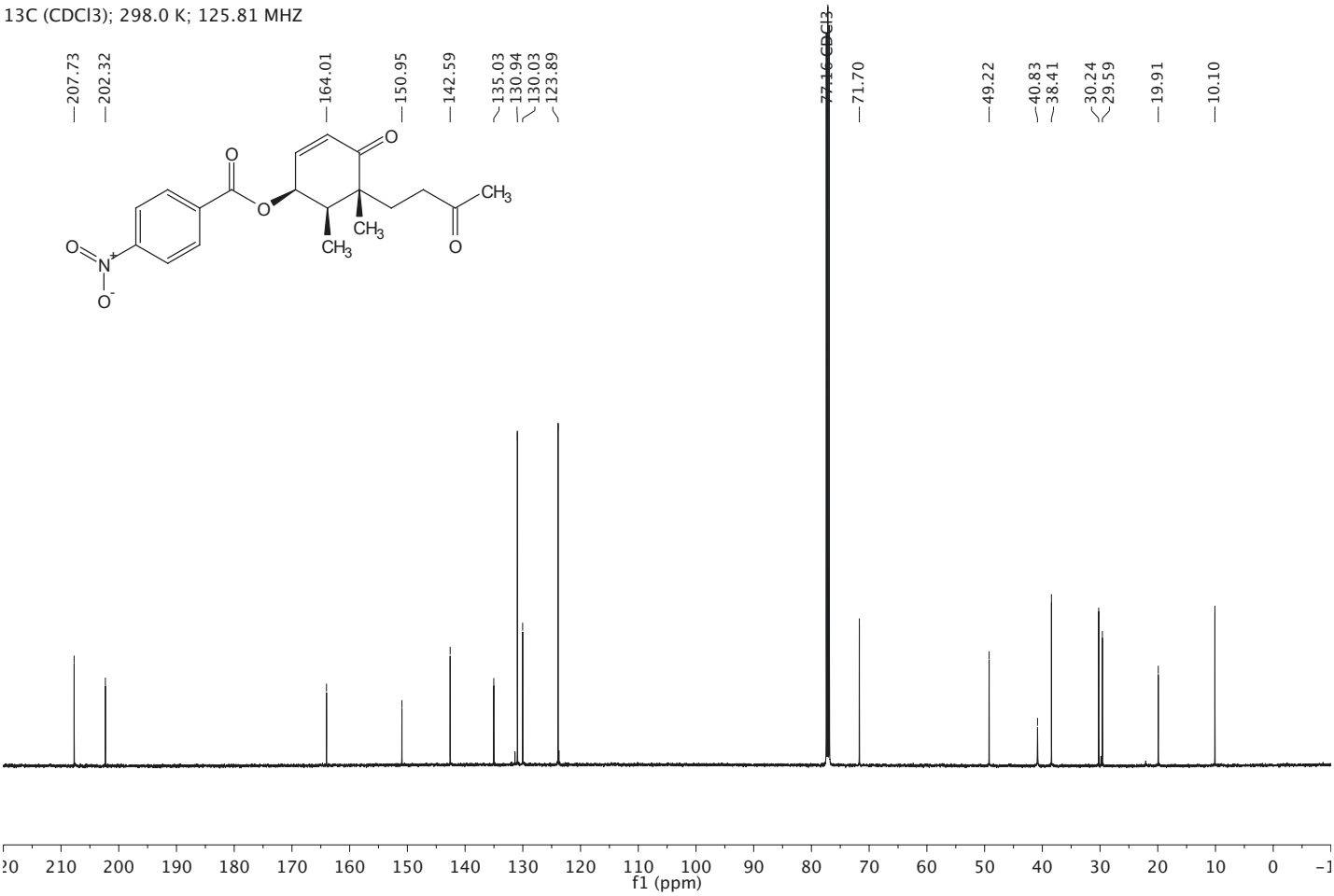
13C (CDCl3); 298.0 K; 125.80 MHZ



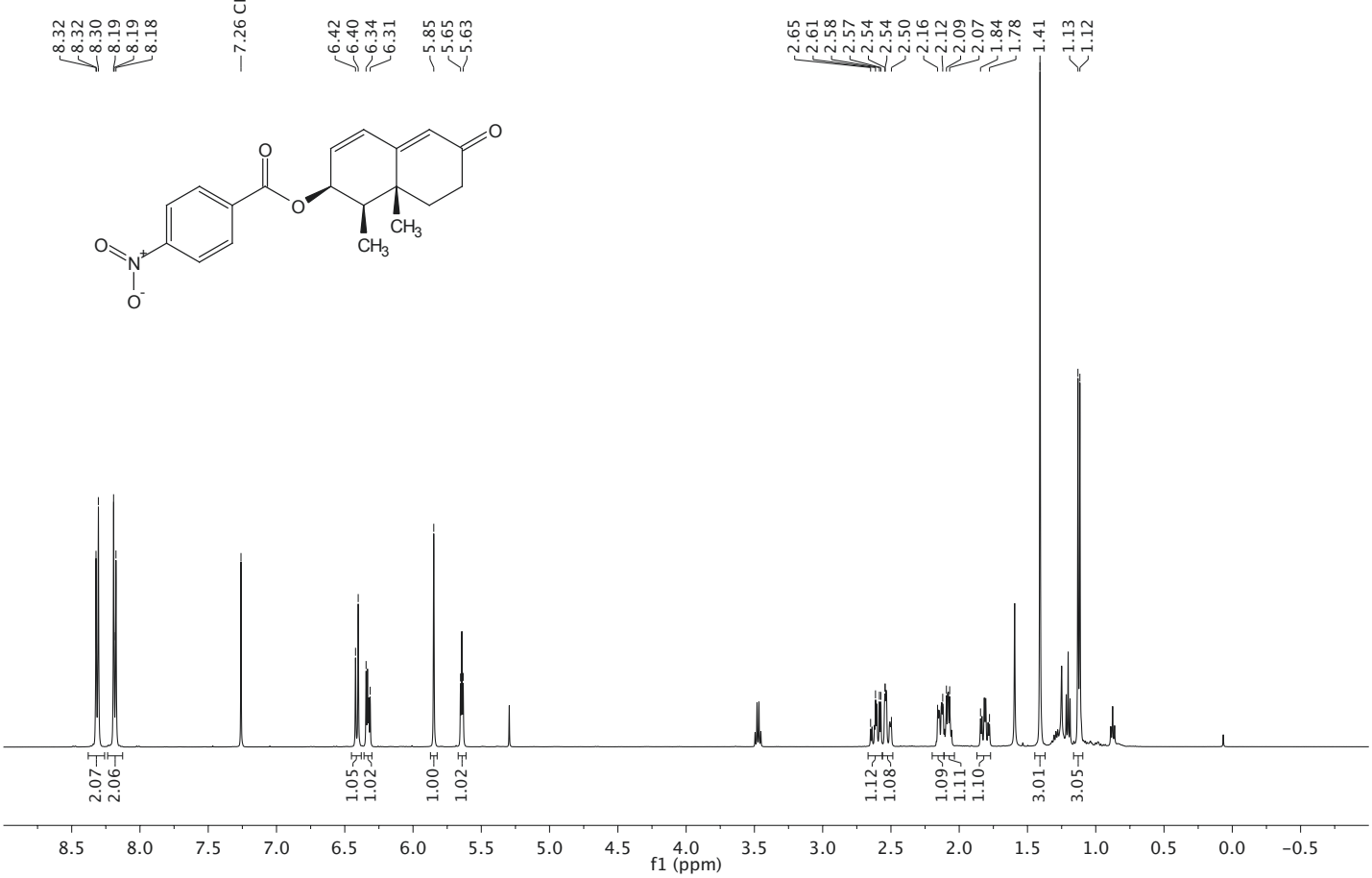
1H (CDCl3); 298.0 K; 500.30 MHZ



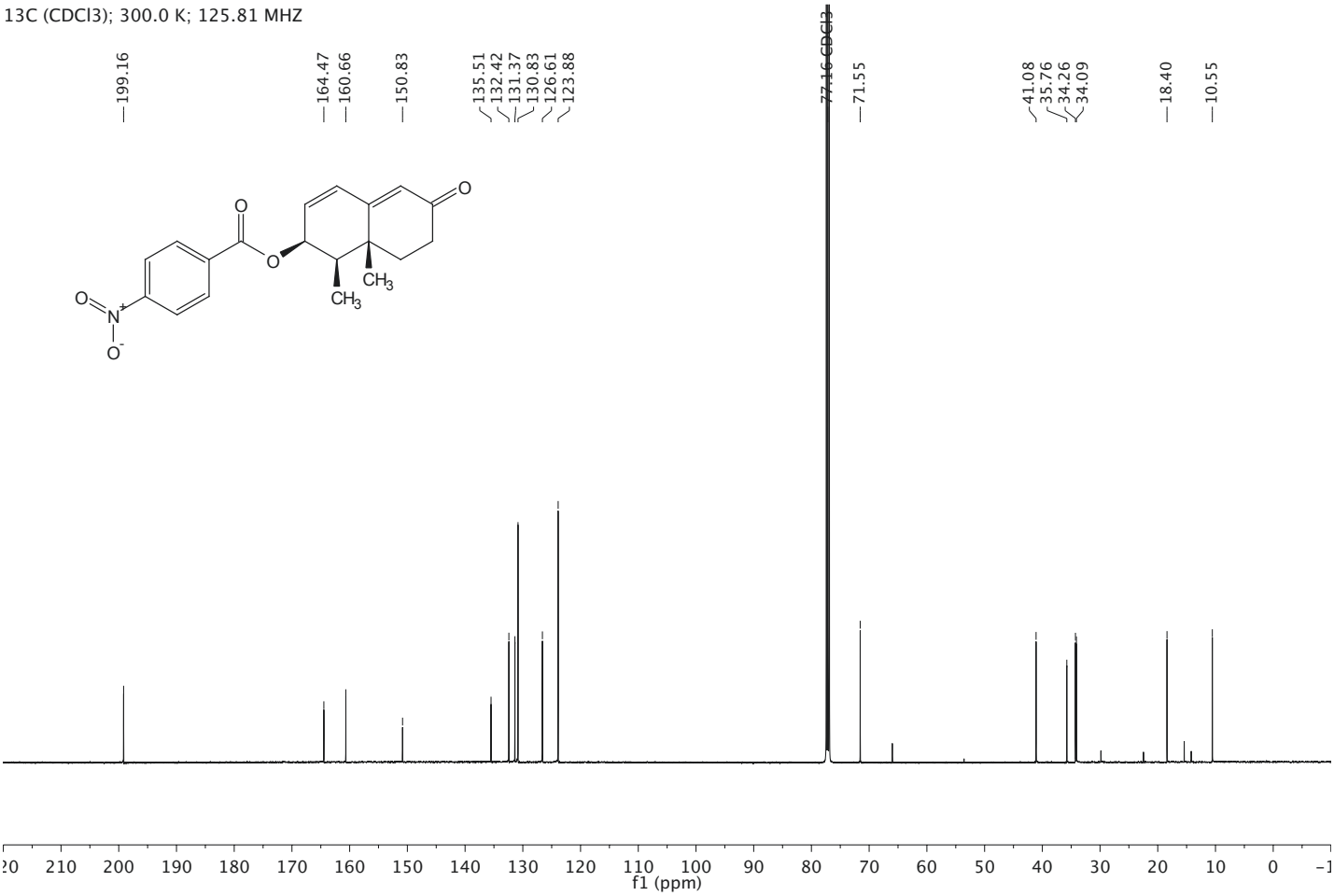
13C (CDCl3); 298.0 K; 125.81 MHZ



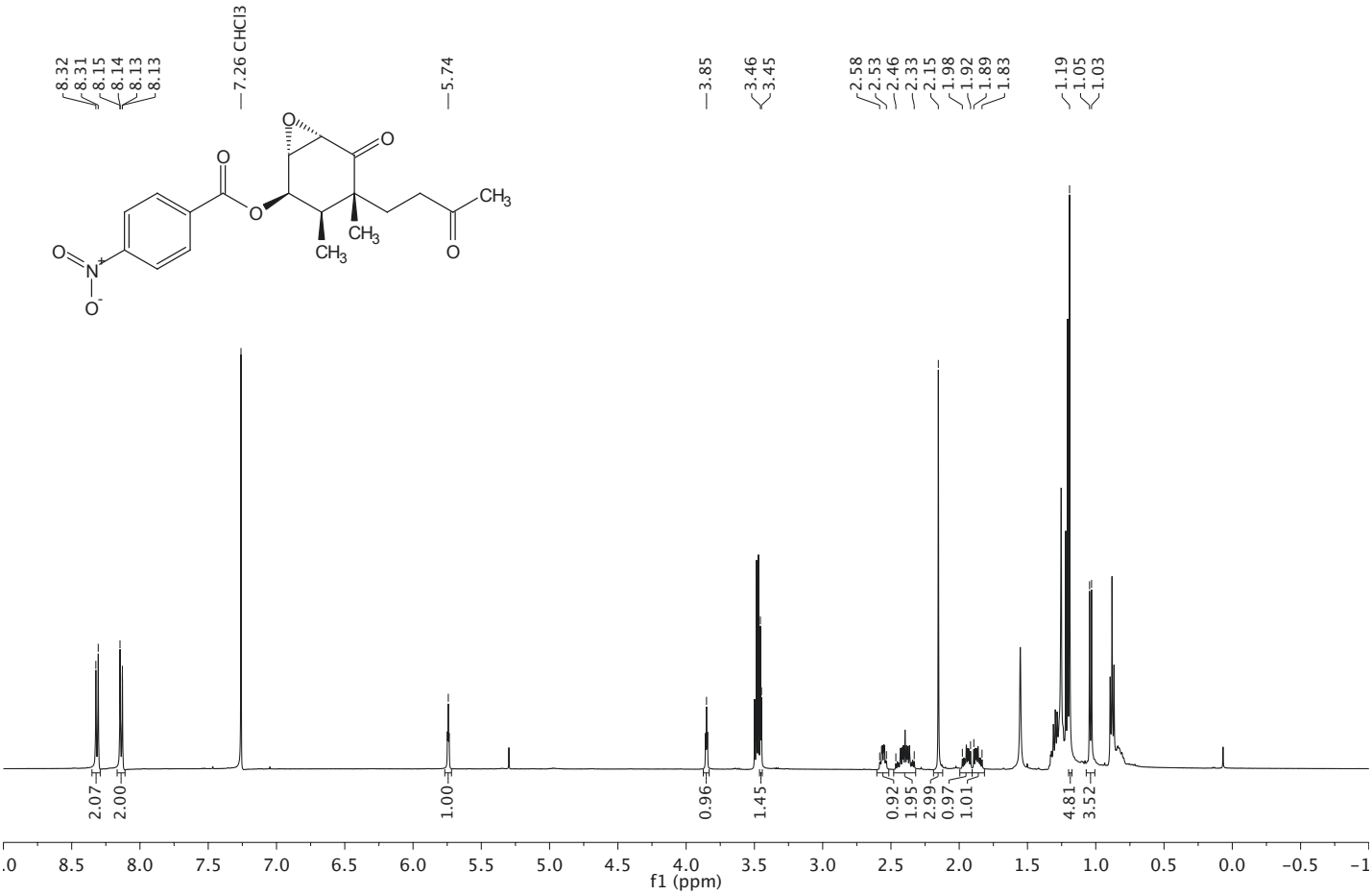
1H (CDCl3); 300.0 K; 500.30 MHZ



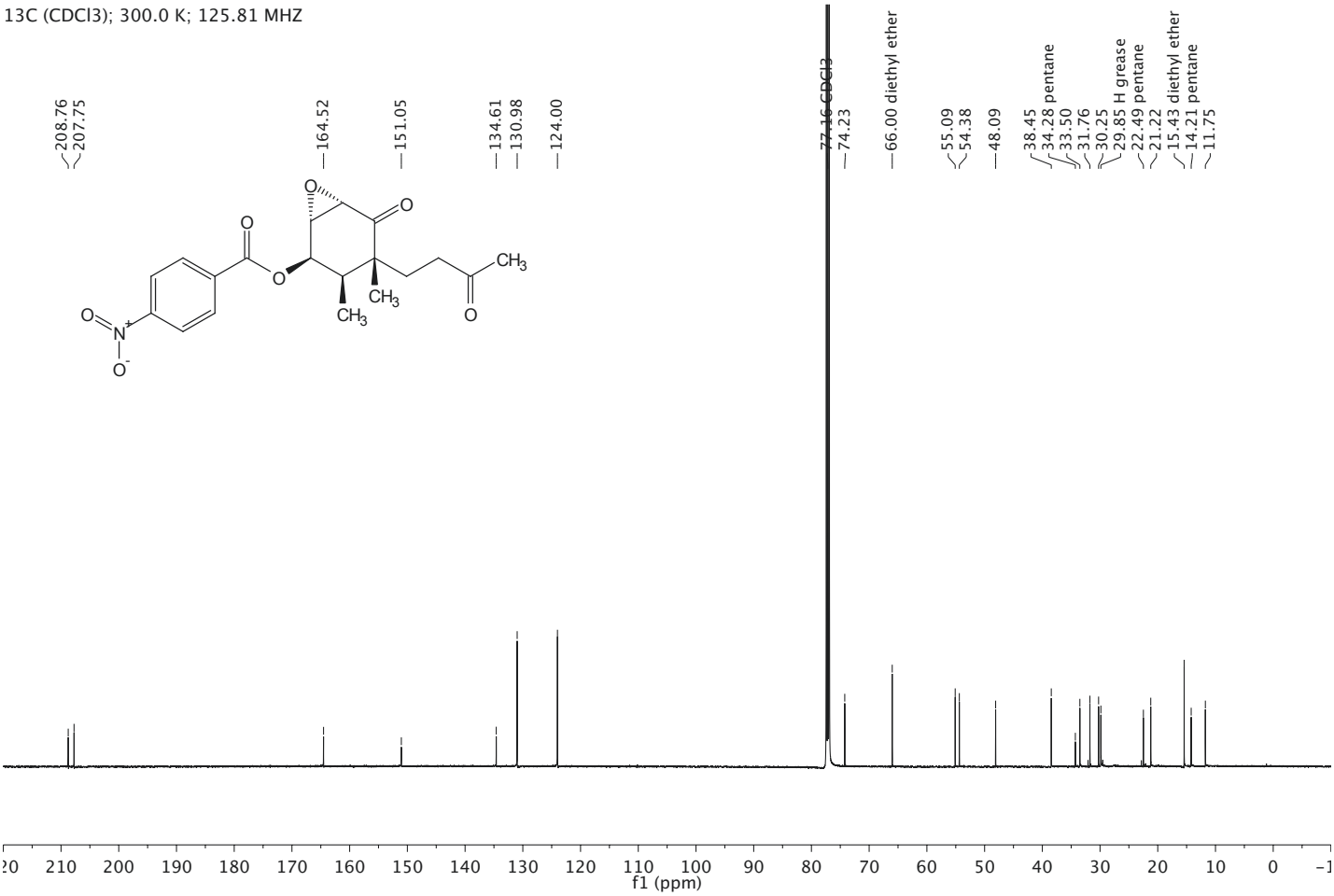
13C (CDCl3); 300.0 K; 125.81 MHZ



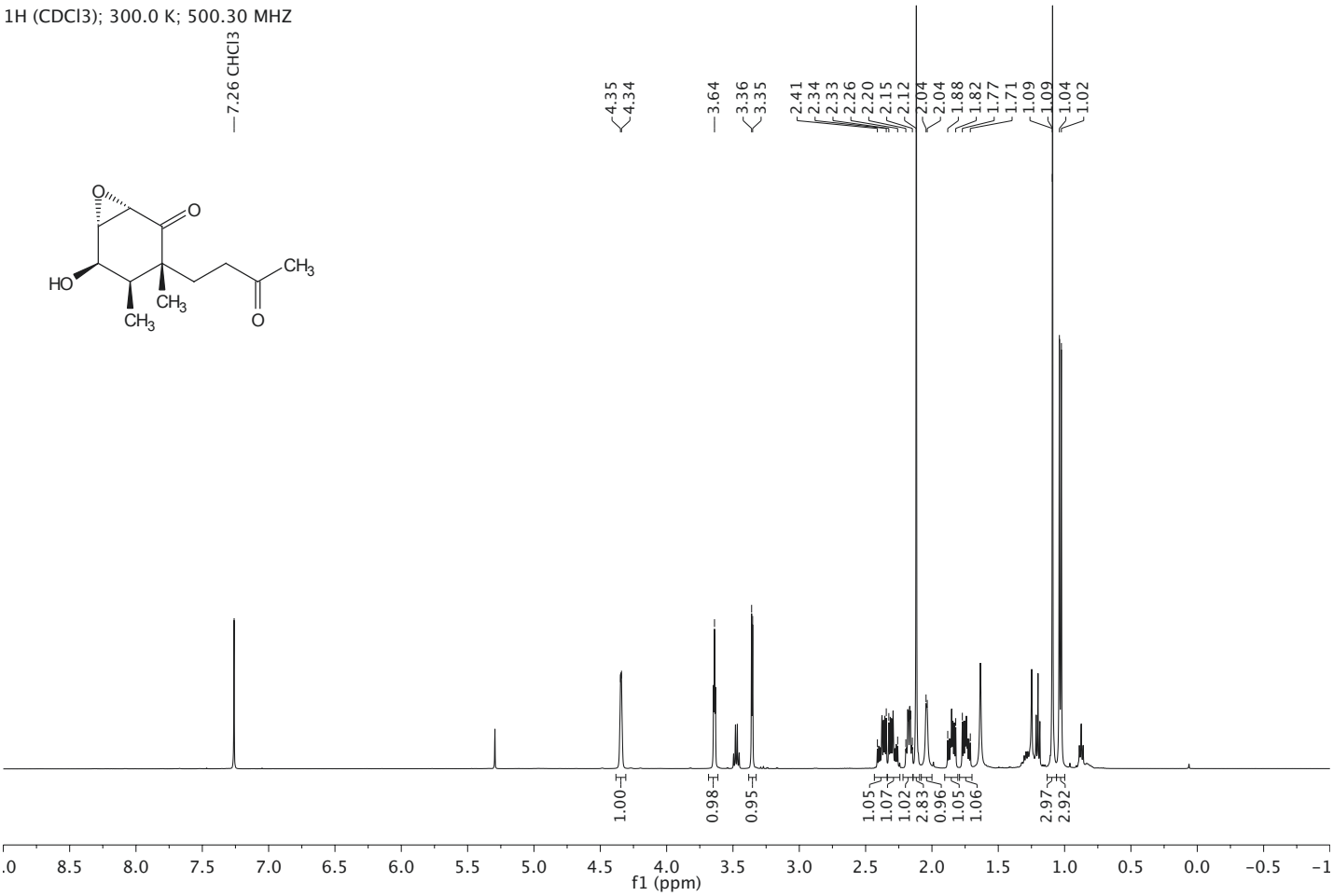
1H (CDCl3); 300.0 K; 500.30 MHZ



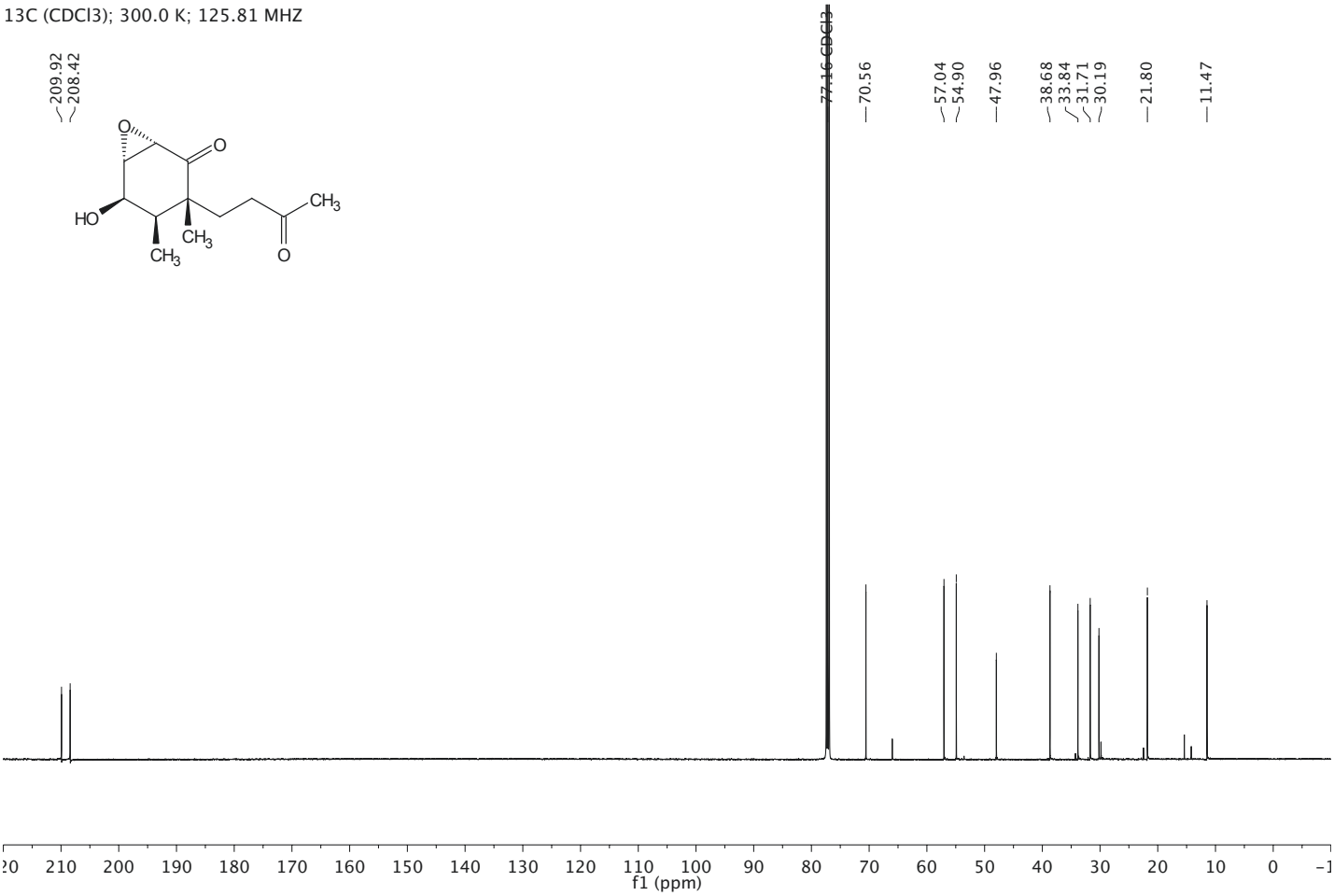
13C (CDCl3); 300.0 K; 125.81 MHZ



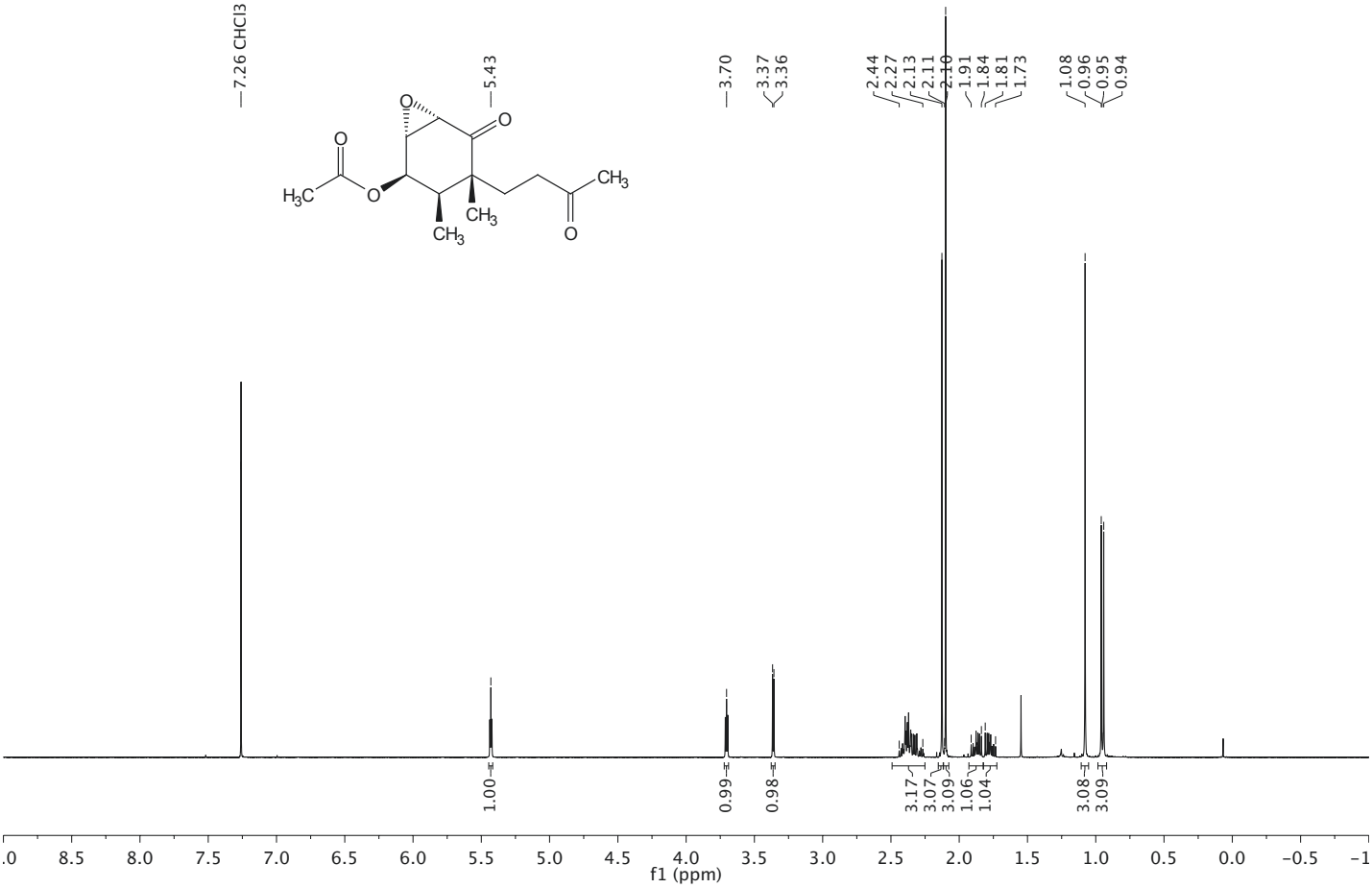
1H (CDCl3); 300.0 K; 500.30 MHZ



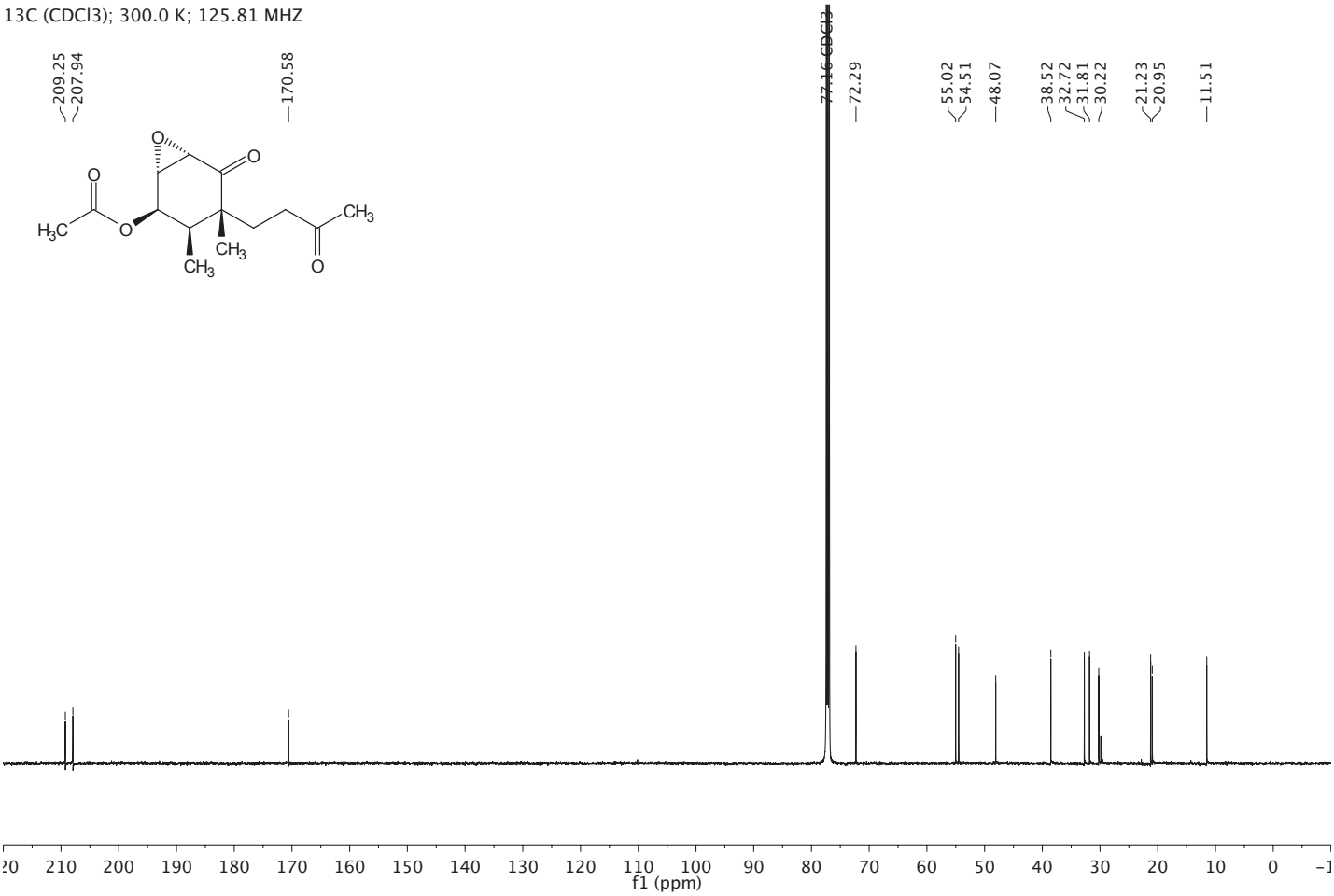
13C (CDCl3); 300.0 K; 125.81 MHZ



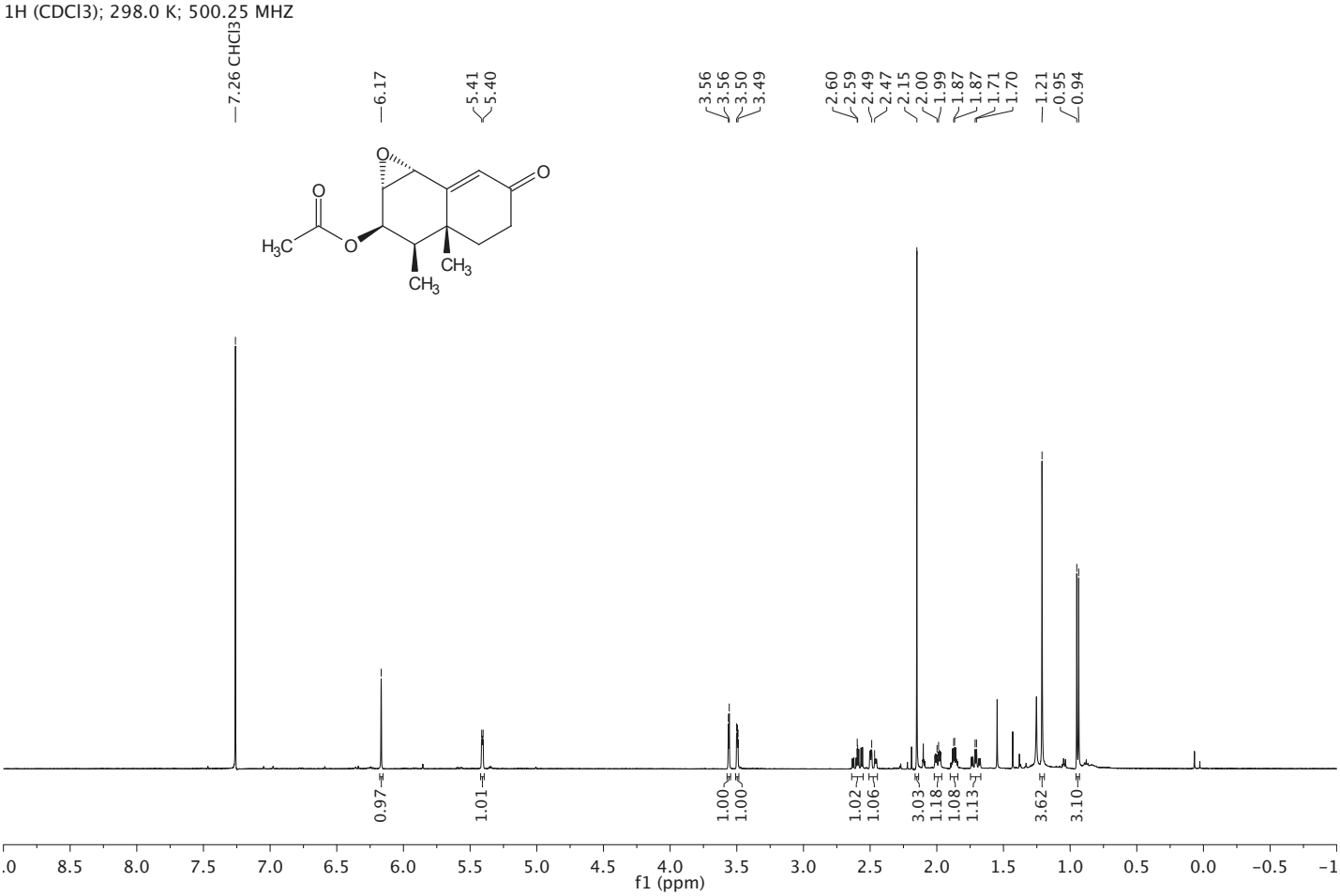
1H (CDCl3); 300.0 K; 400.13 MHZ



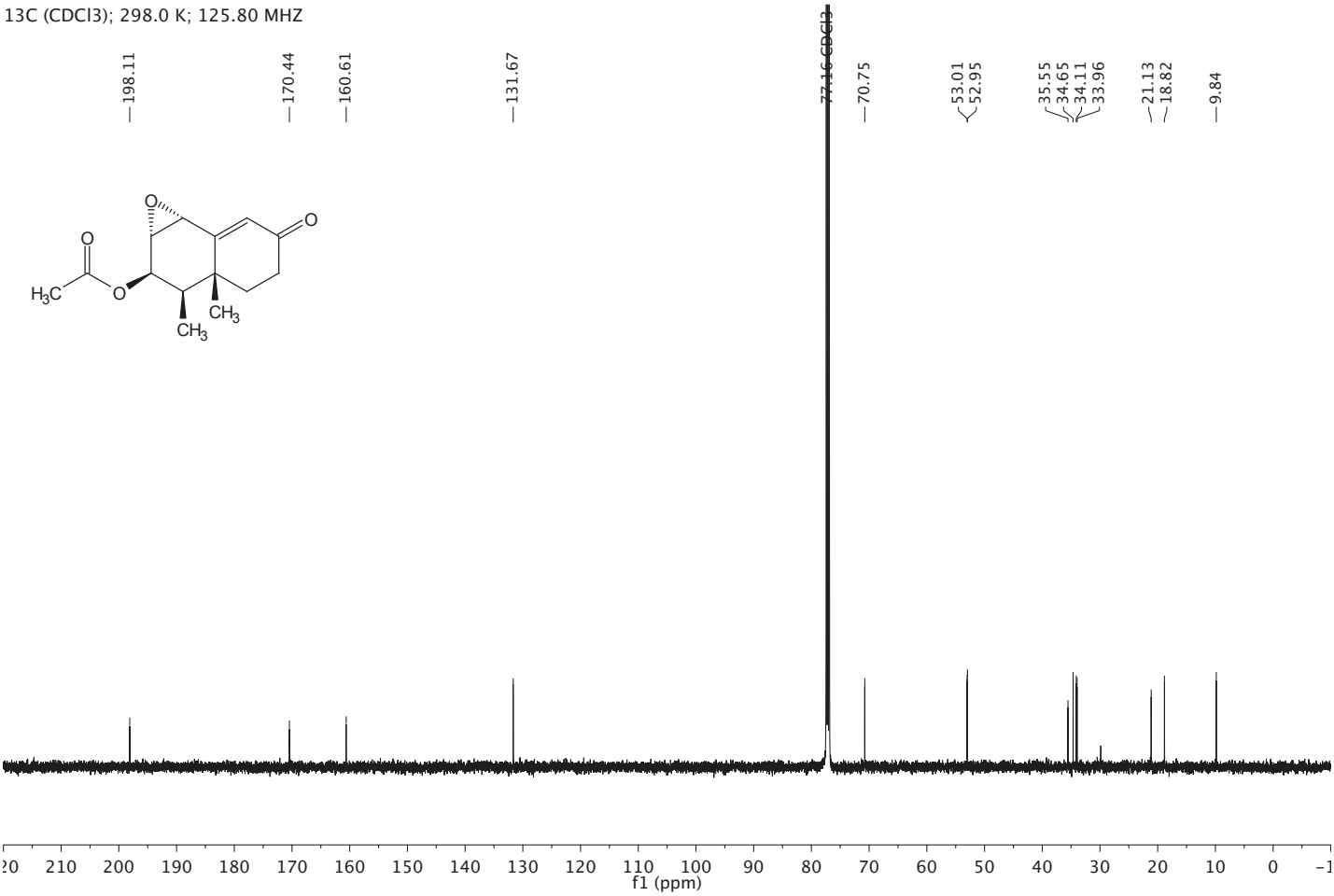
13C (CDCl3); 300.0 K; 125.81 MHZ



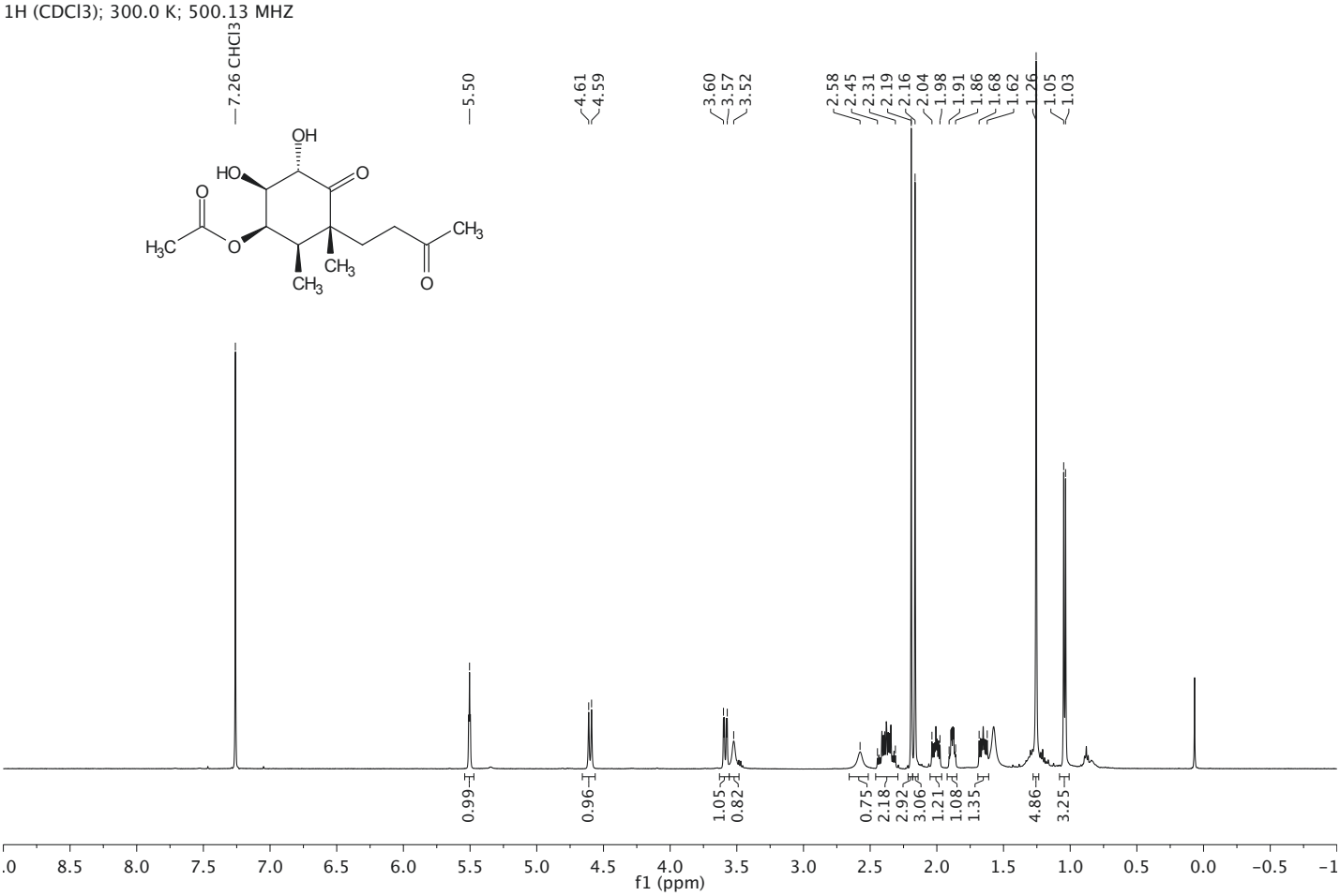
1H (CDCl3); 298.0 K; 500.25 MHZ



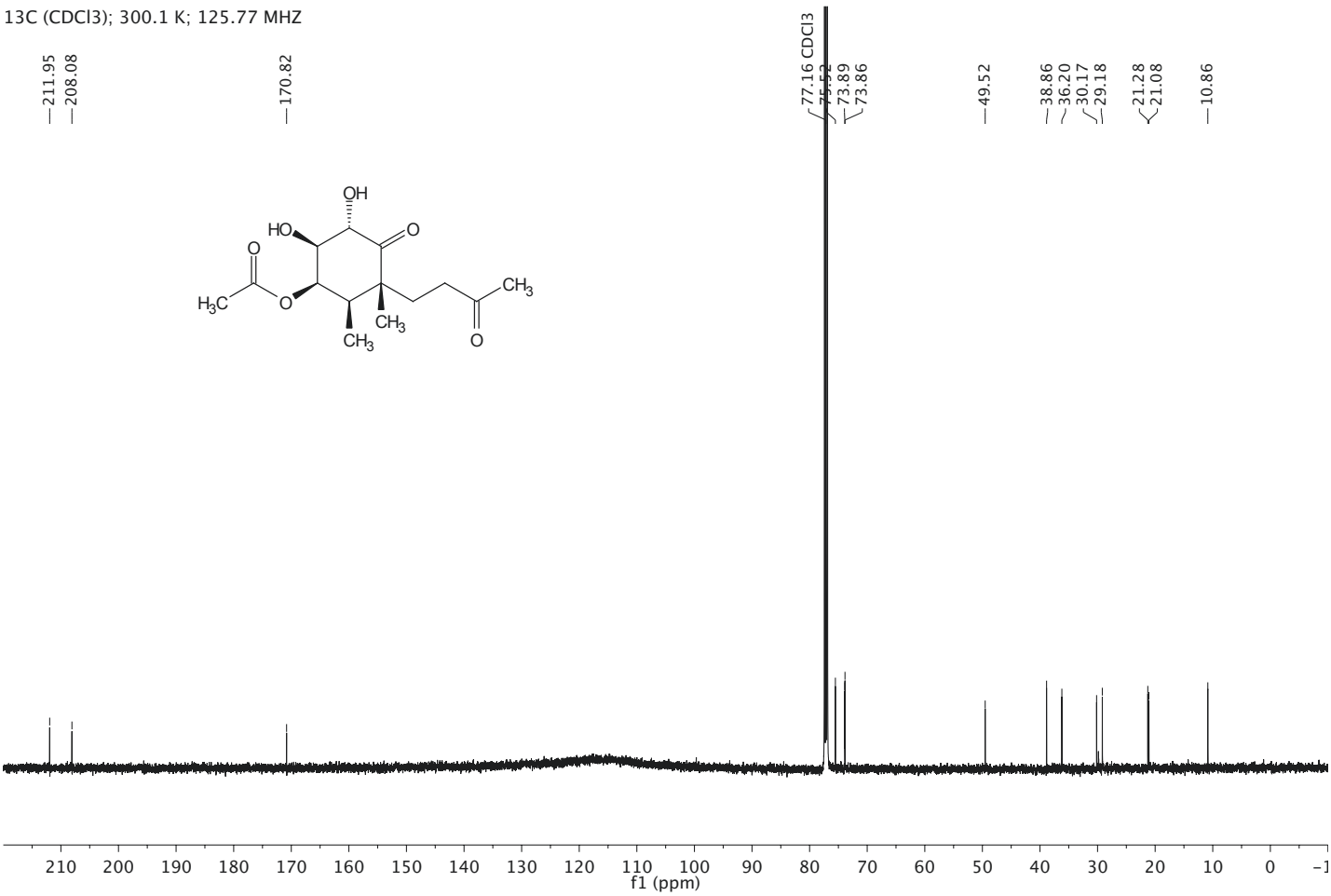
13C (CDCl3); 298.0 K; 125.80 MHZ



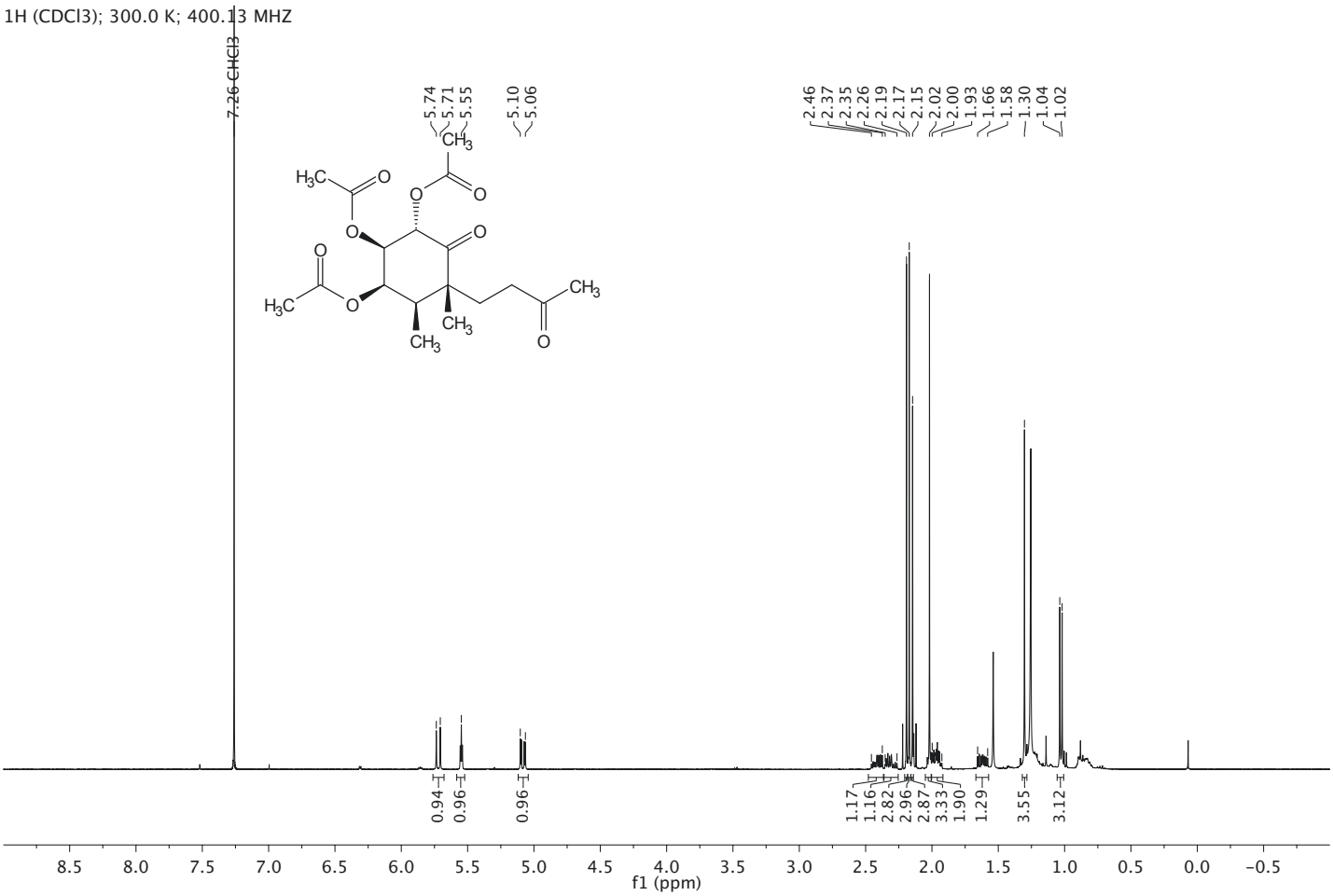
1H (CDCl3); 300.0 K; 500.13 MHZ



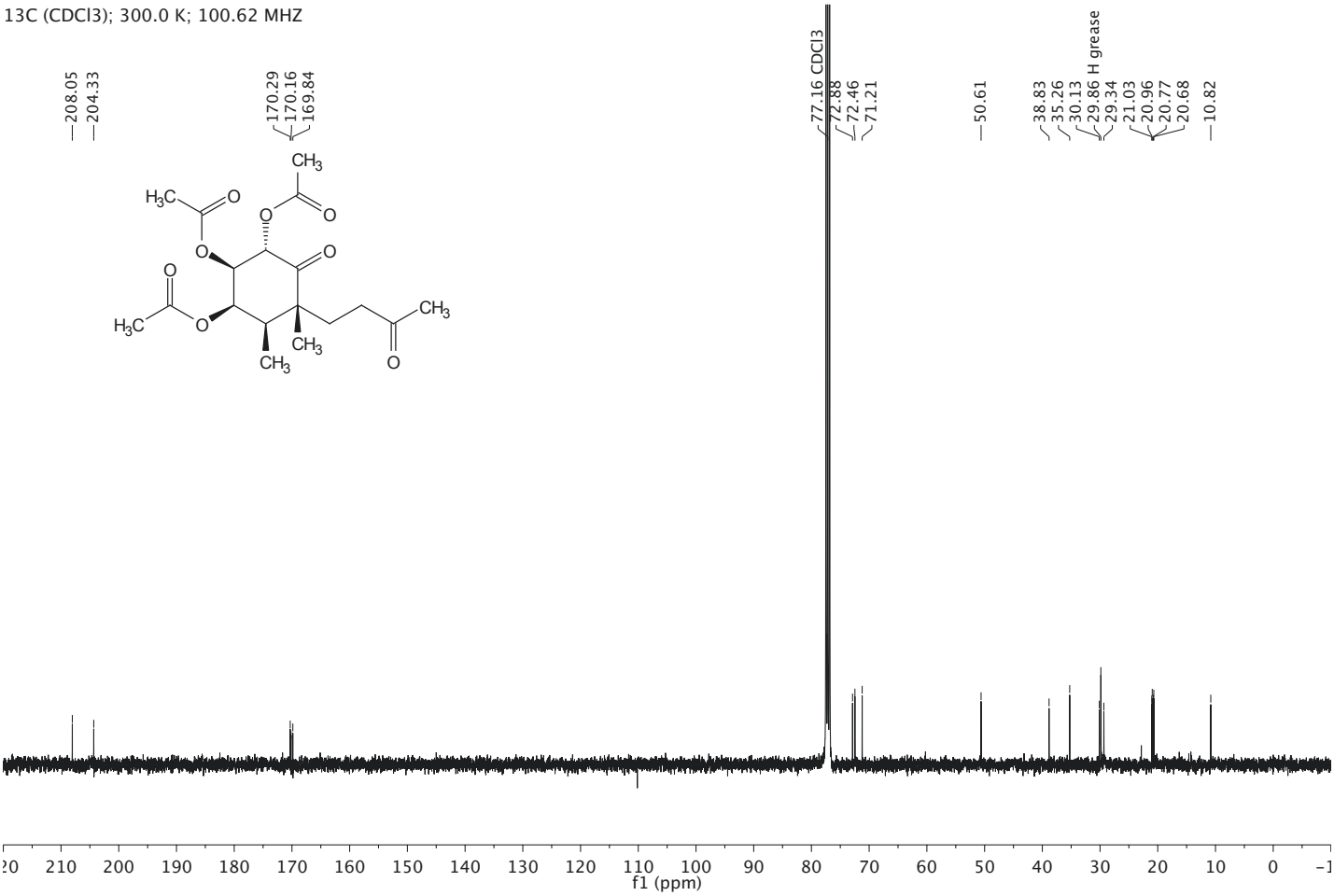
13C (CDCl3); 300.1 K; 125.77 MHZ



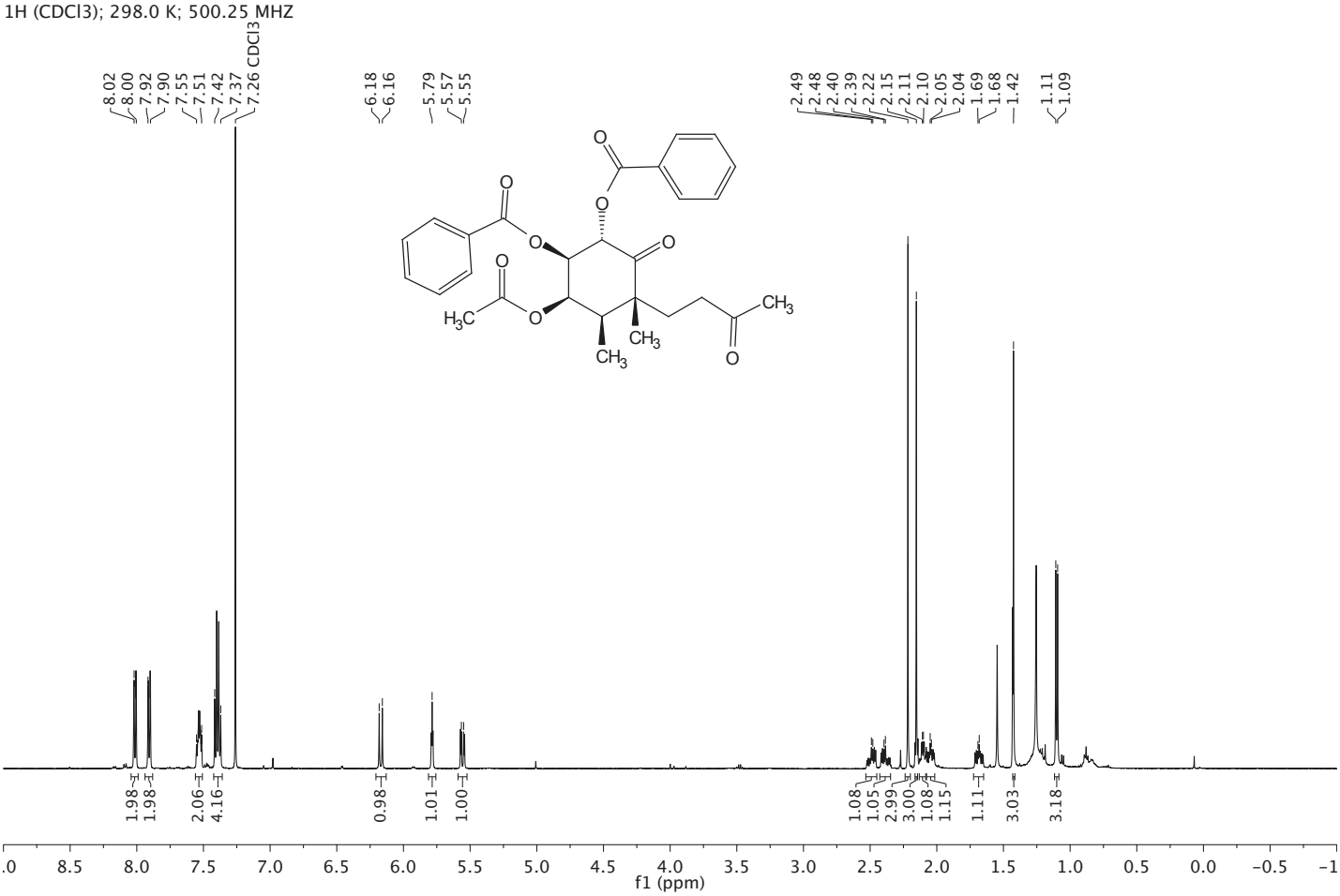
1H (CDCl3); 300.0 K; 400.13 MHZ



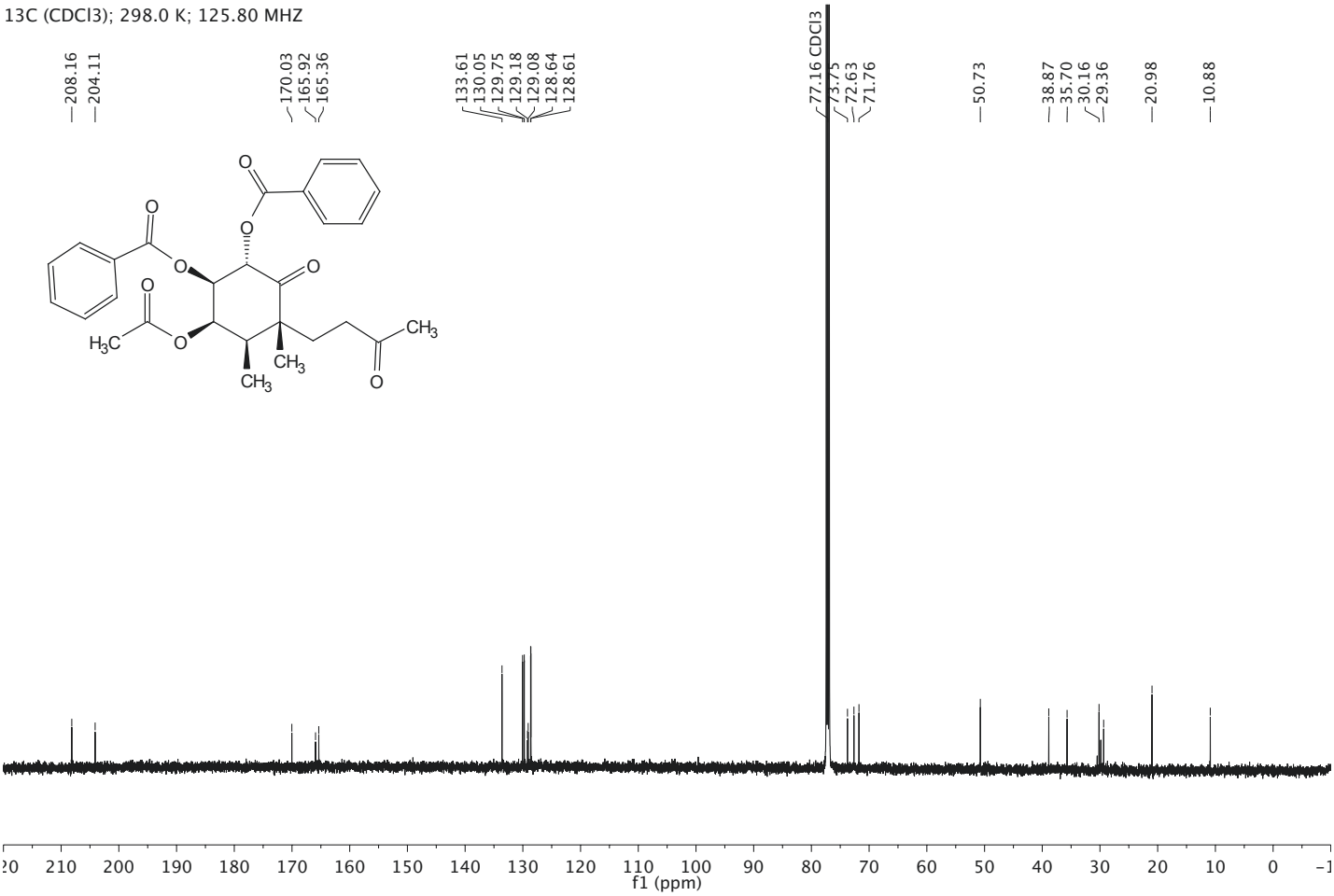
13C (CDCl3); 300.0 K; 100.62 MHZ



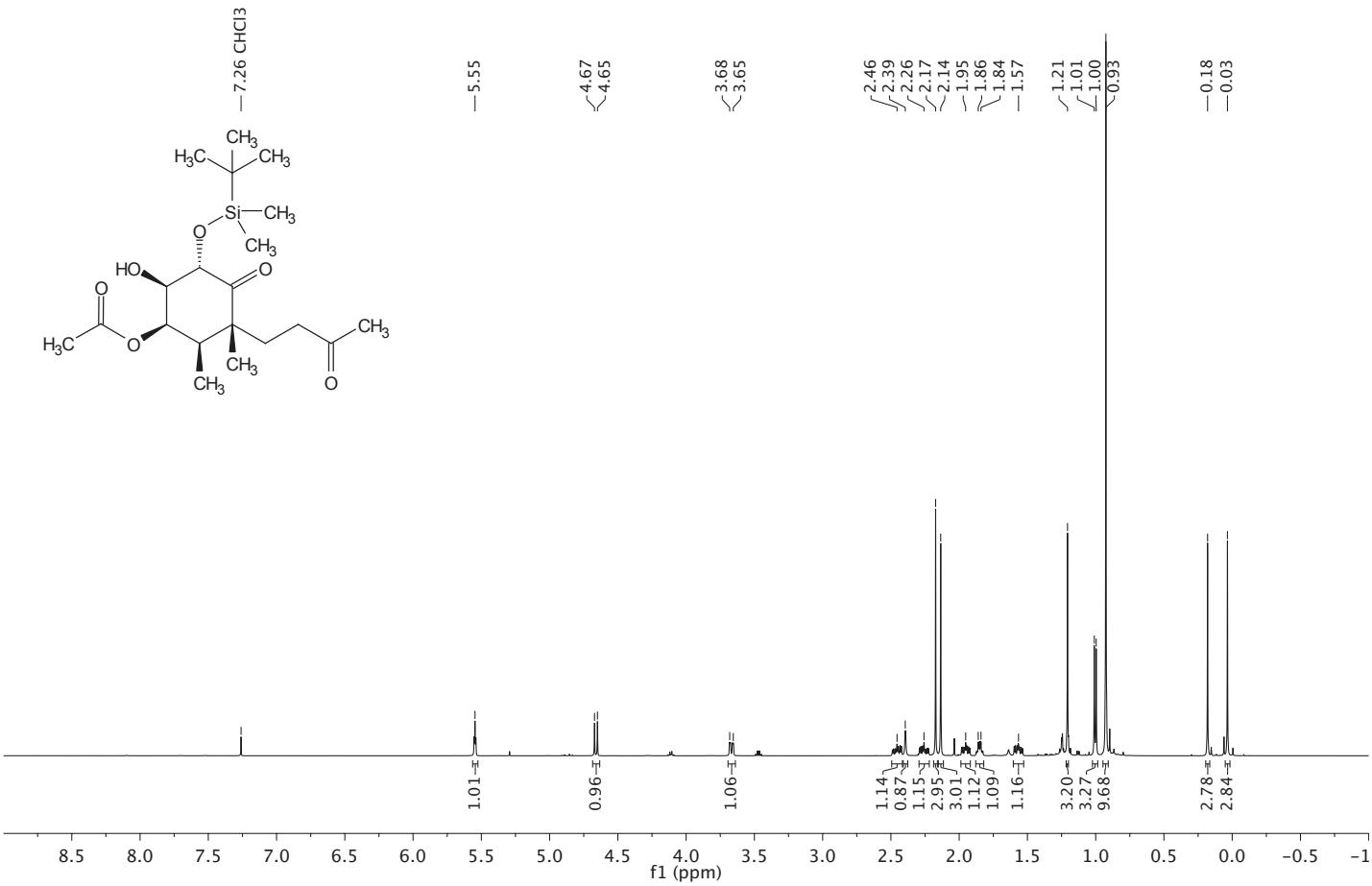
1H (CDCl3); 298.0 K; 500.25 MHZ



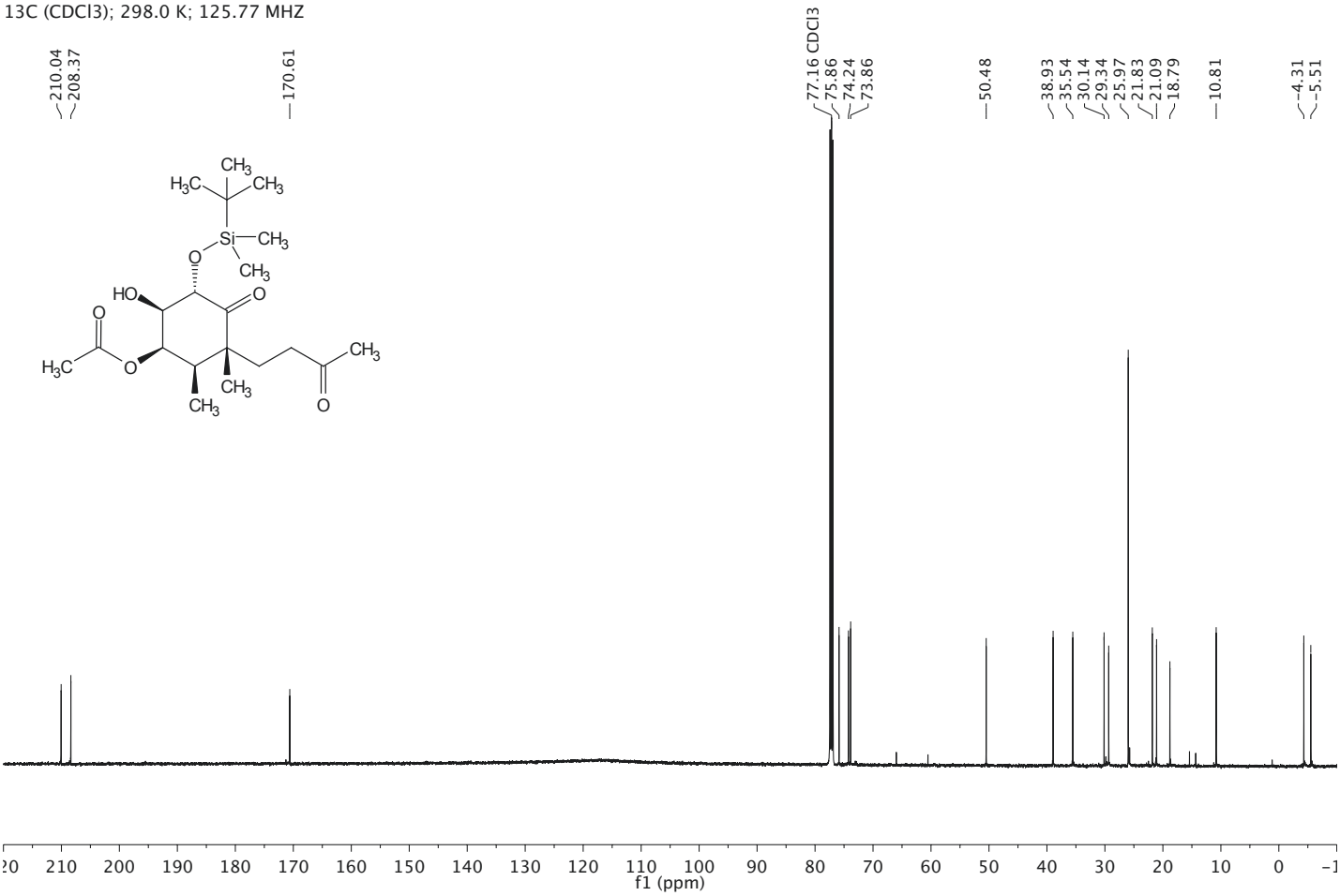
13C (CDCl3); 298.0 K; 125.80 MHZ



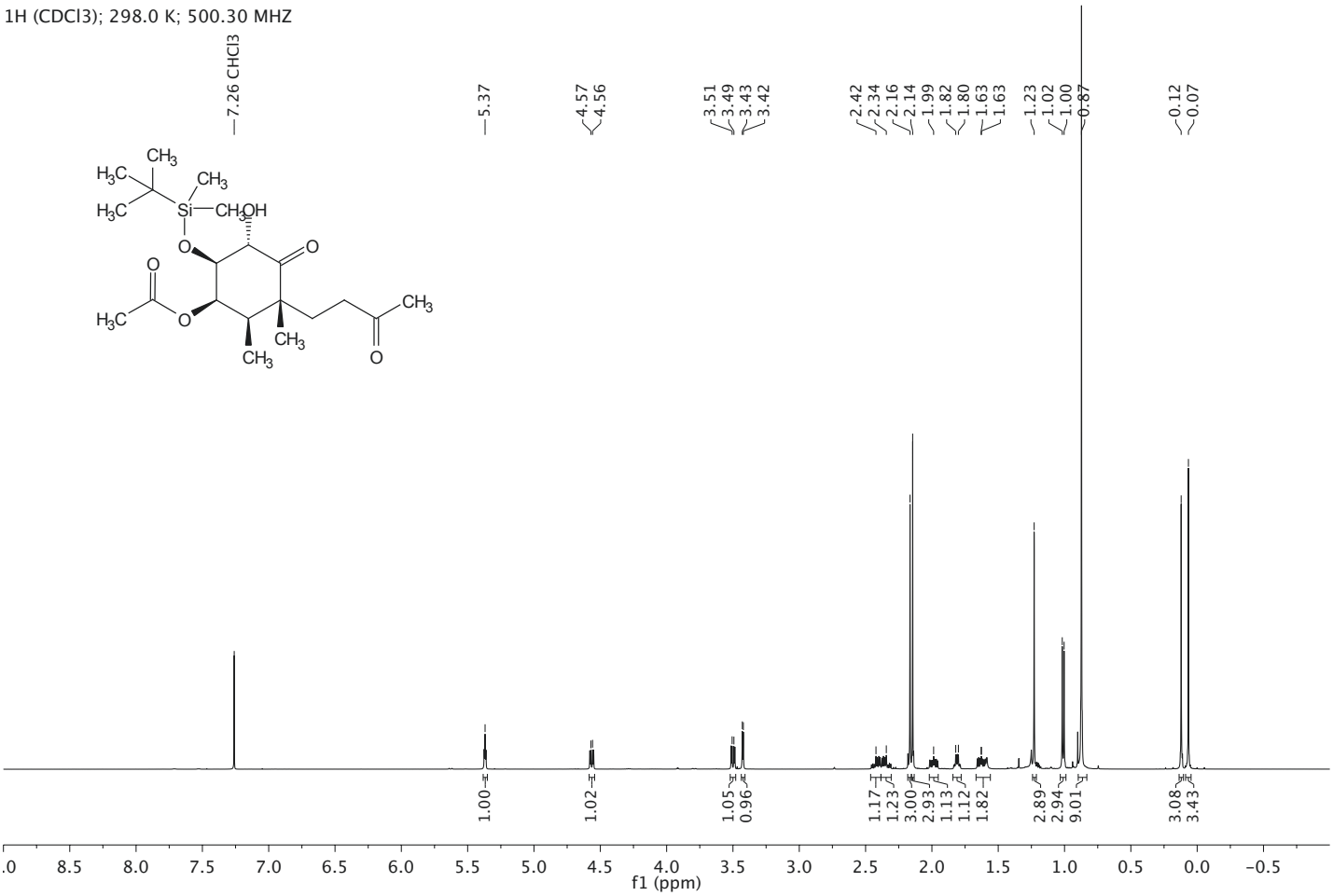
1H (CDCl3); 298.0 K; 500.13 MHZ



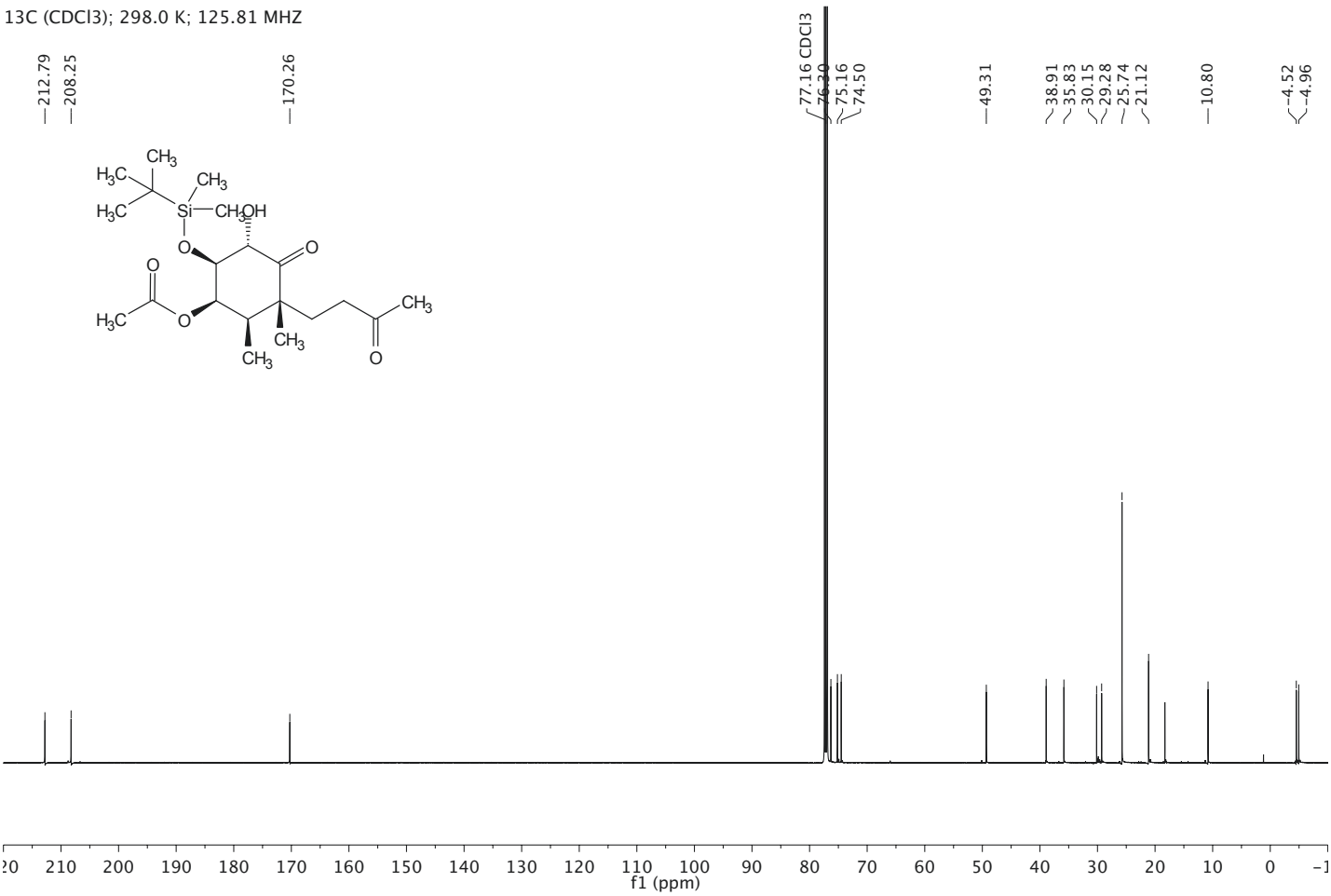
13C (CDCl3); 298.0 K; 125.77 MHZ



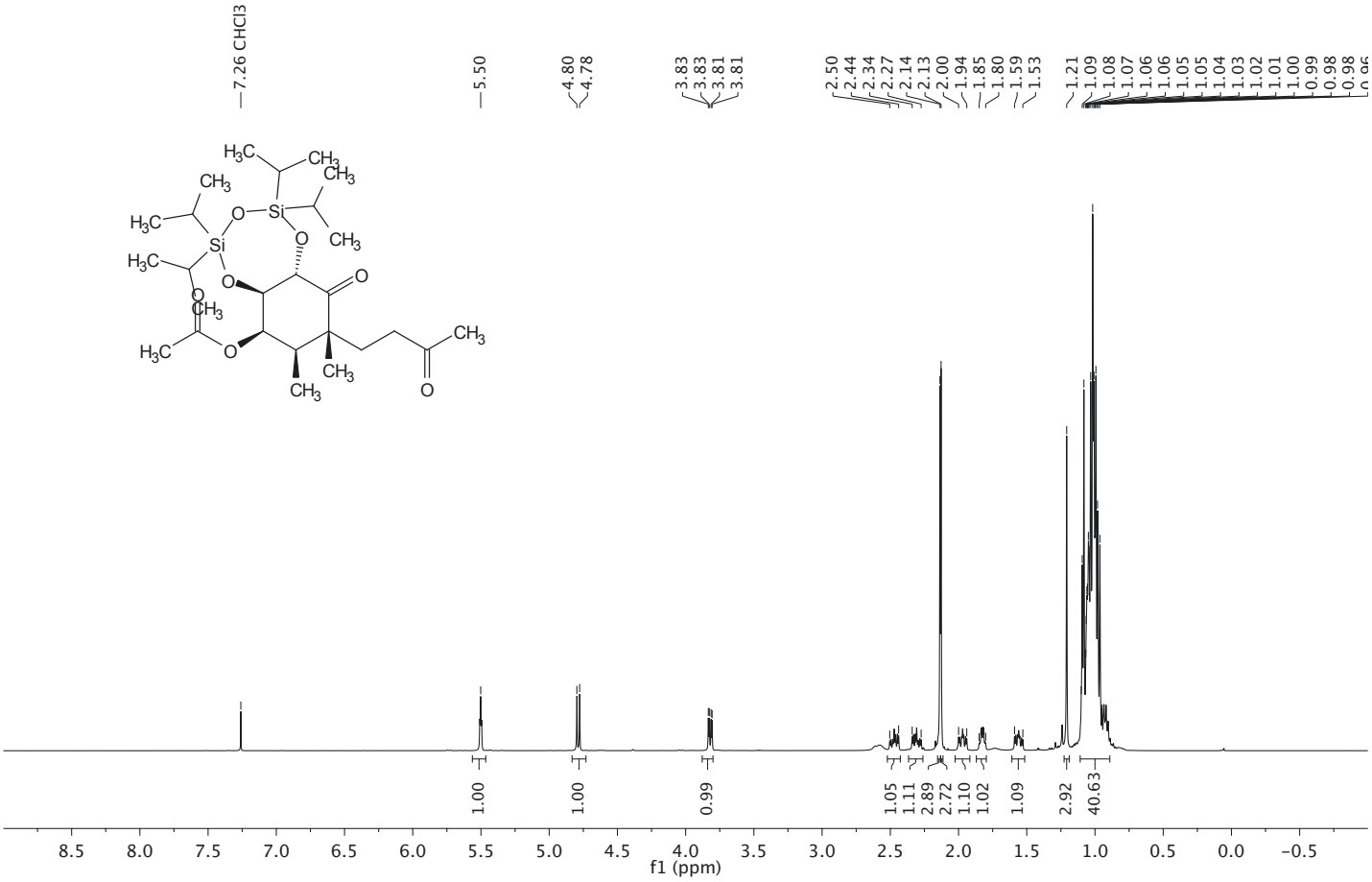
1H (CDCl3); 298.0 K; 500.30 MHZ



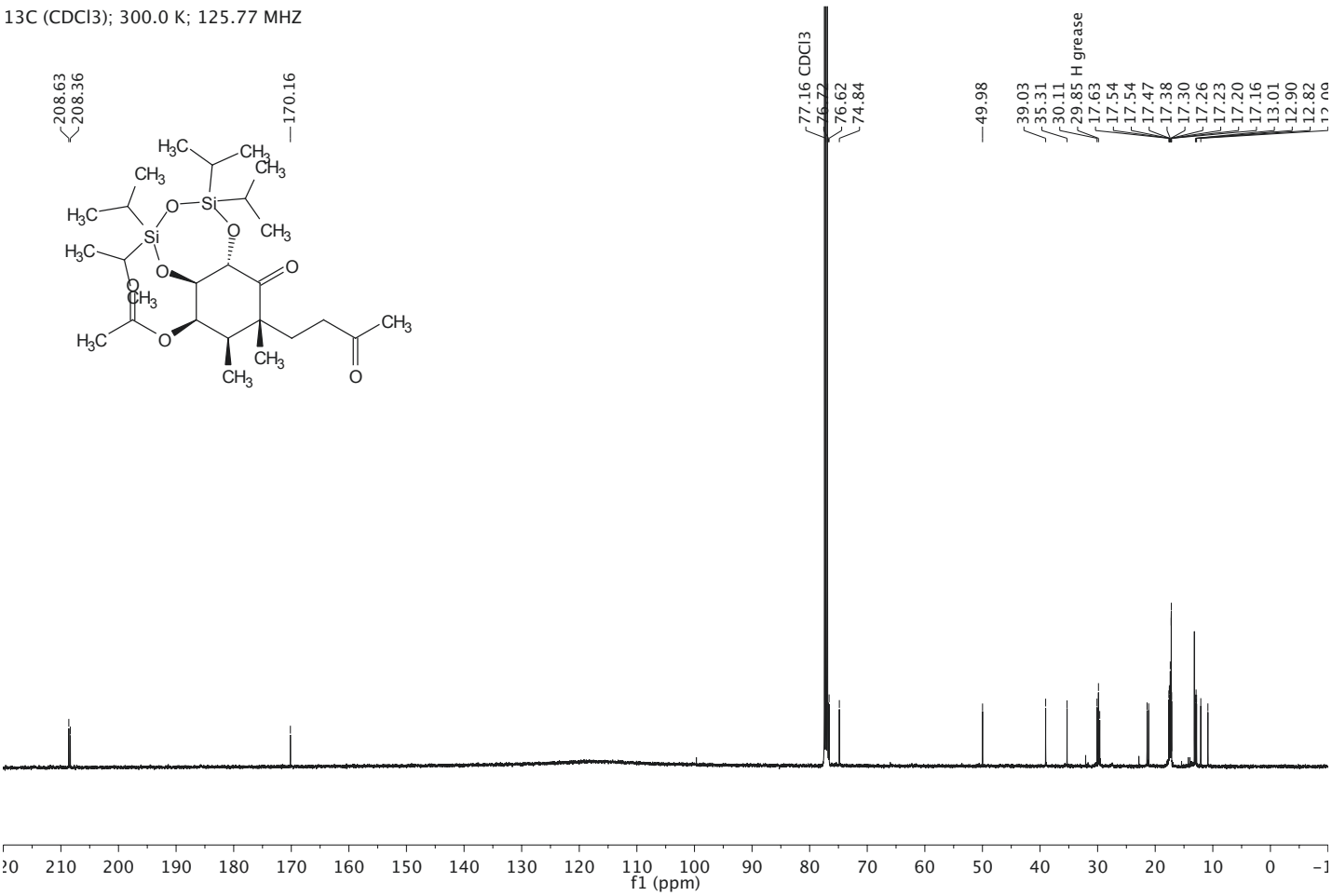
13C (CDCl3); 298.0 K; 125.81 MHZ



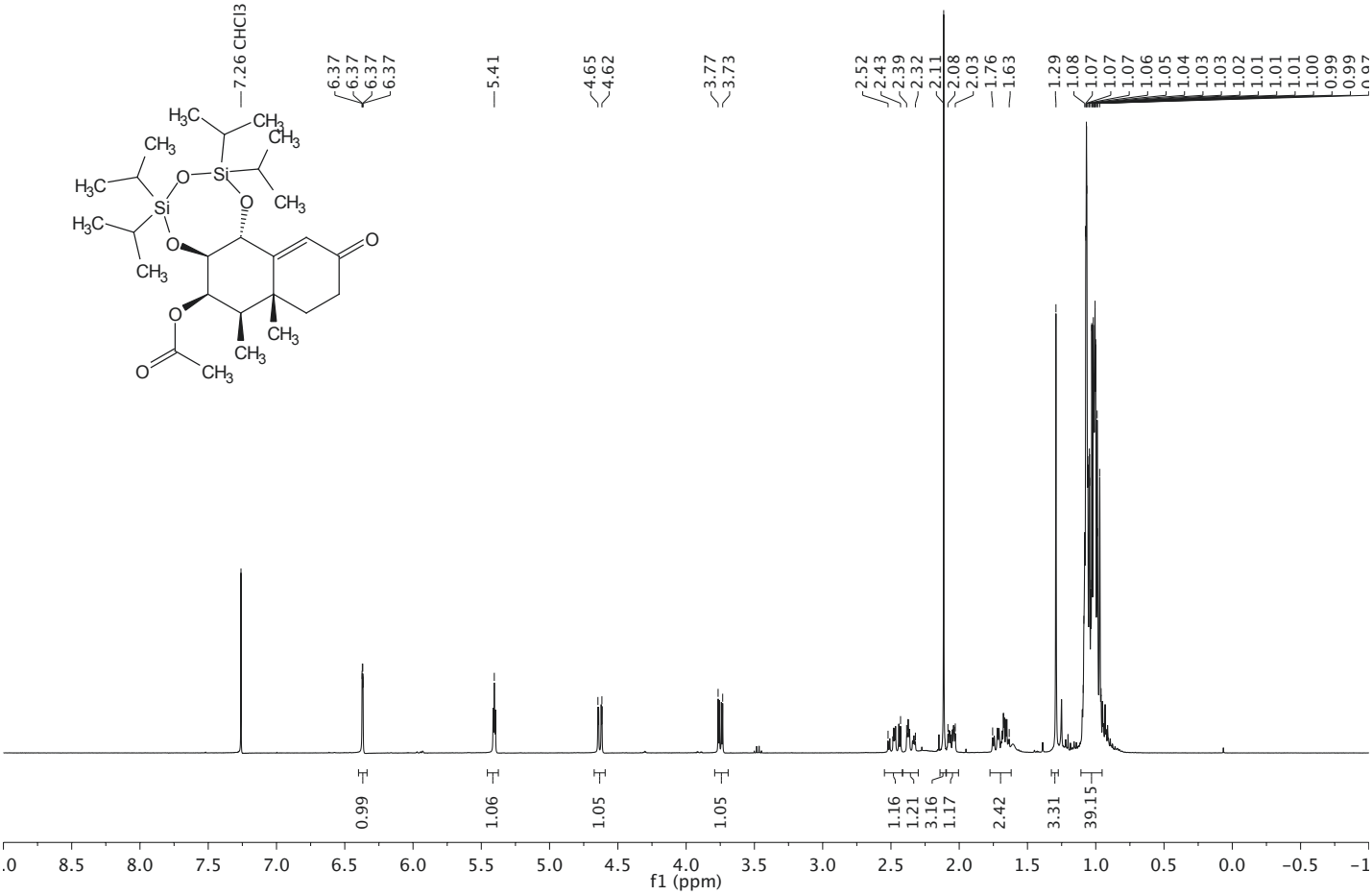
1H (CDCl3); 300.0 K; 500.30 MHZ



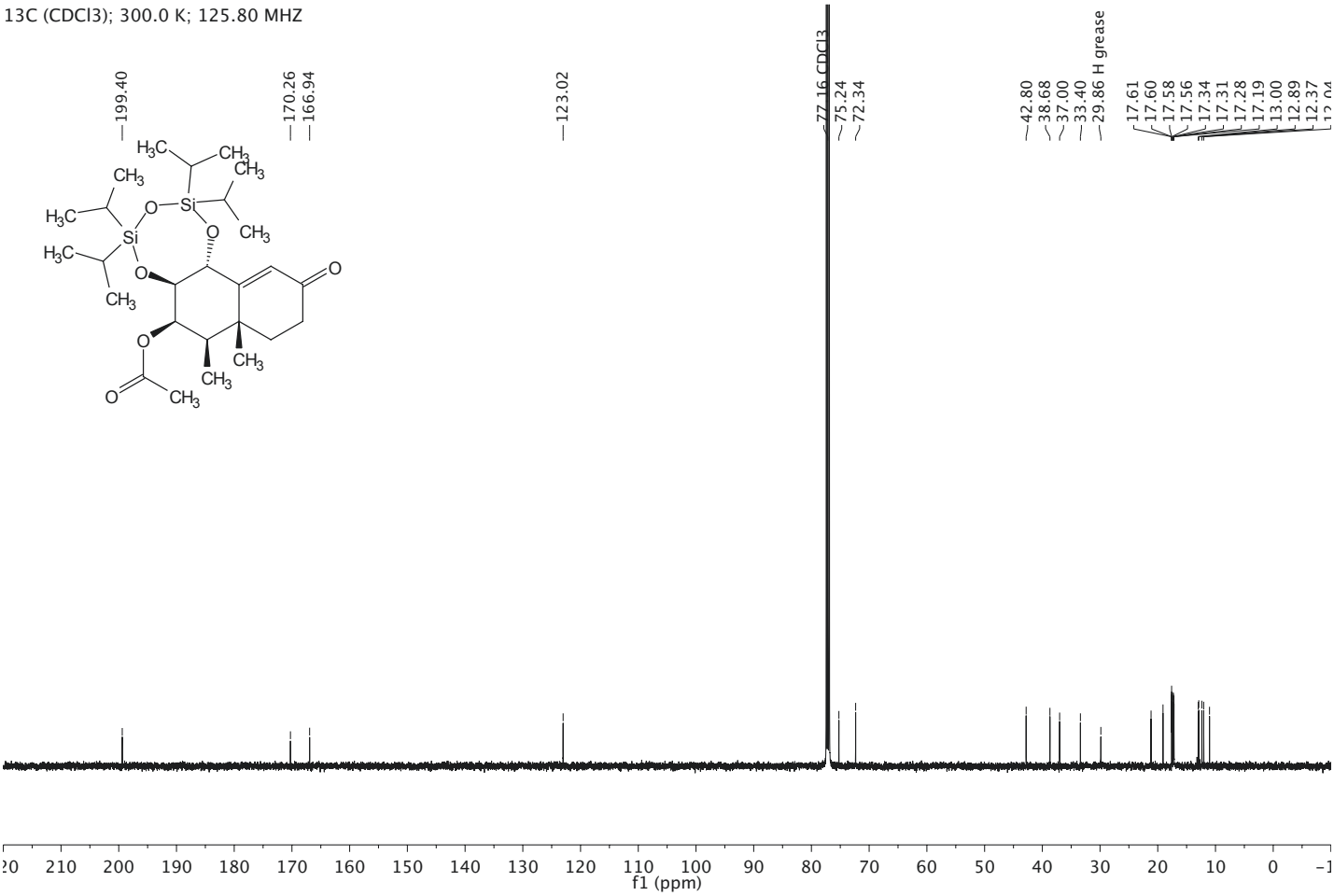
13C (CDCl3); 300.0 K; 125.77 MHZ



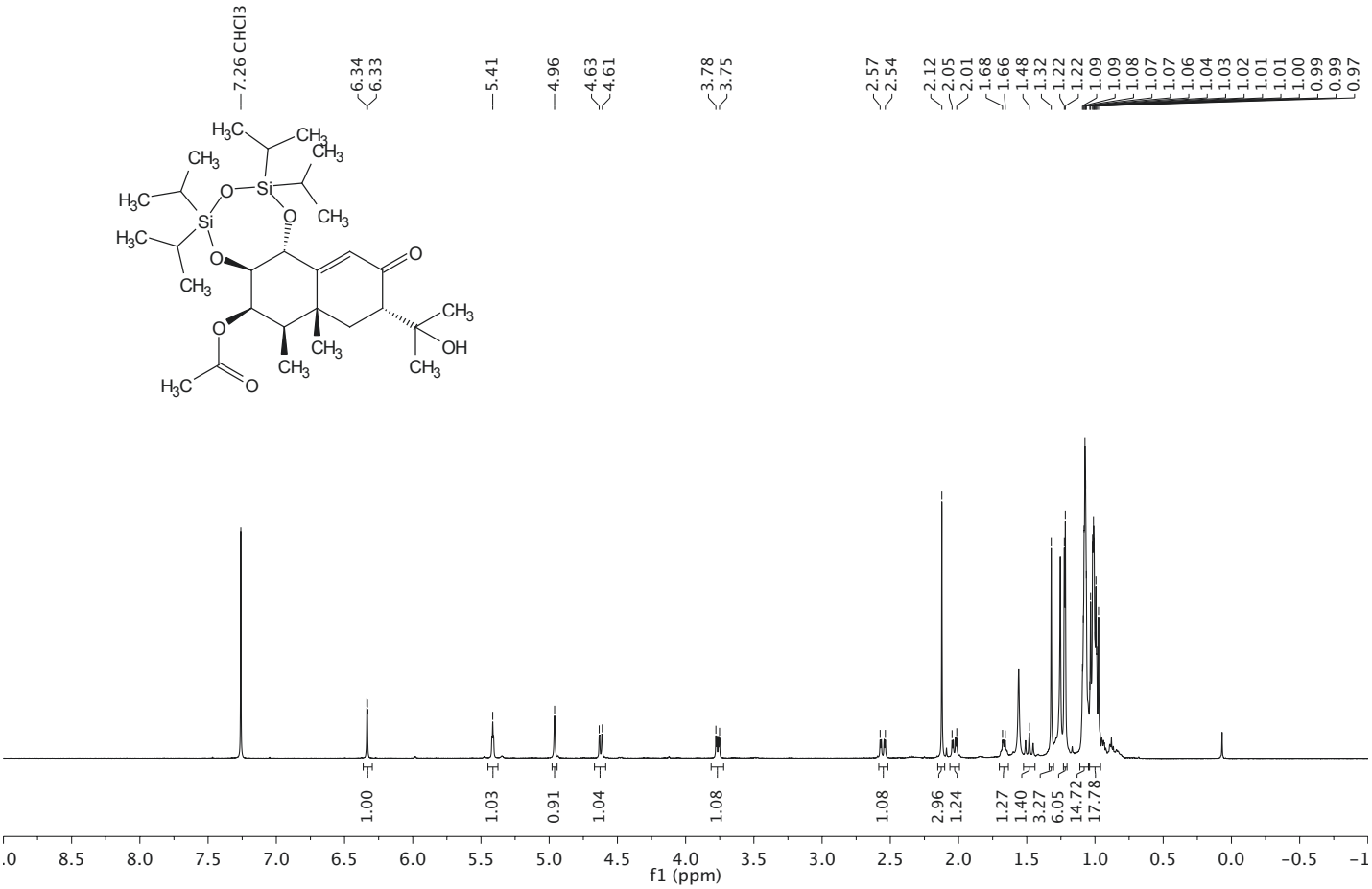
1H (CDCl3); 300.0 K; 400.23 MHZ



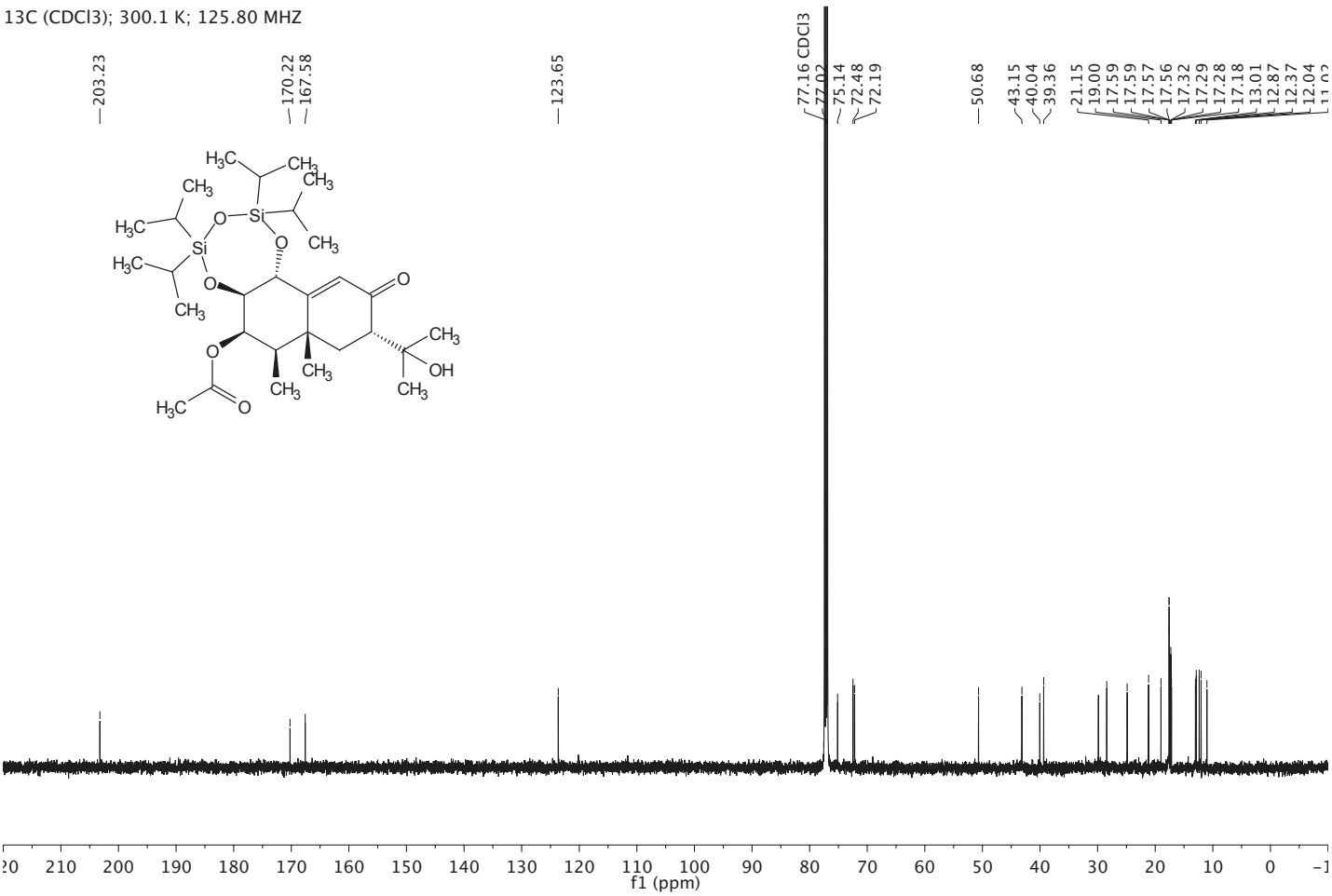
13C (CDCl3); 300.0 K; 125.80 MHZ



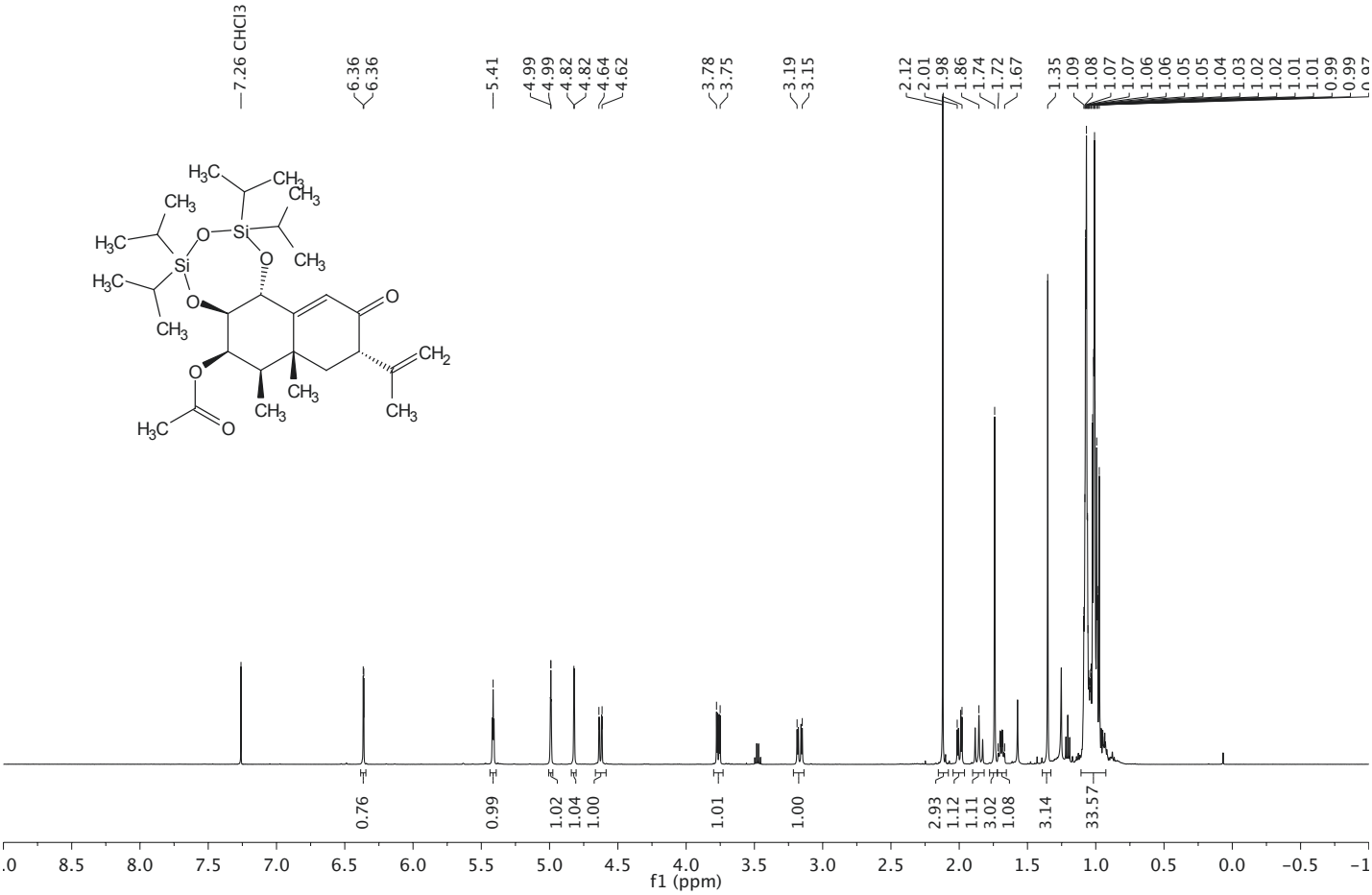
1H (CDCl3); 300.0 K; 500.25 MHZ



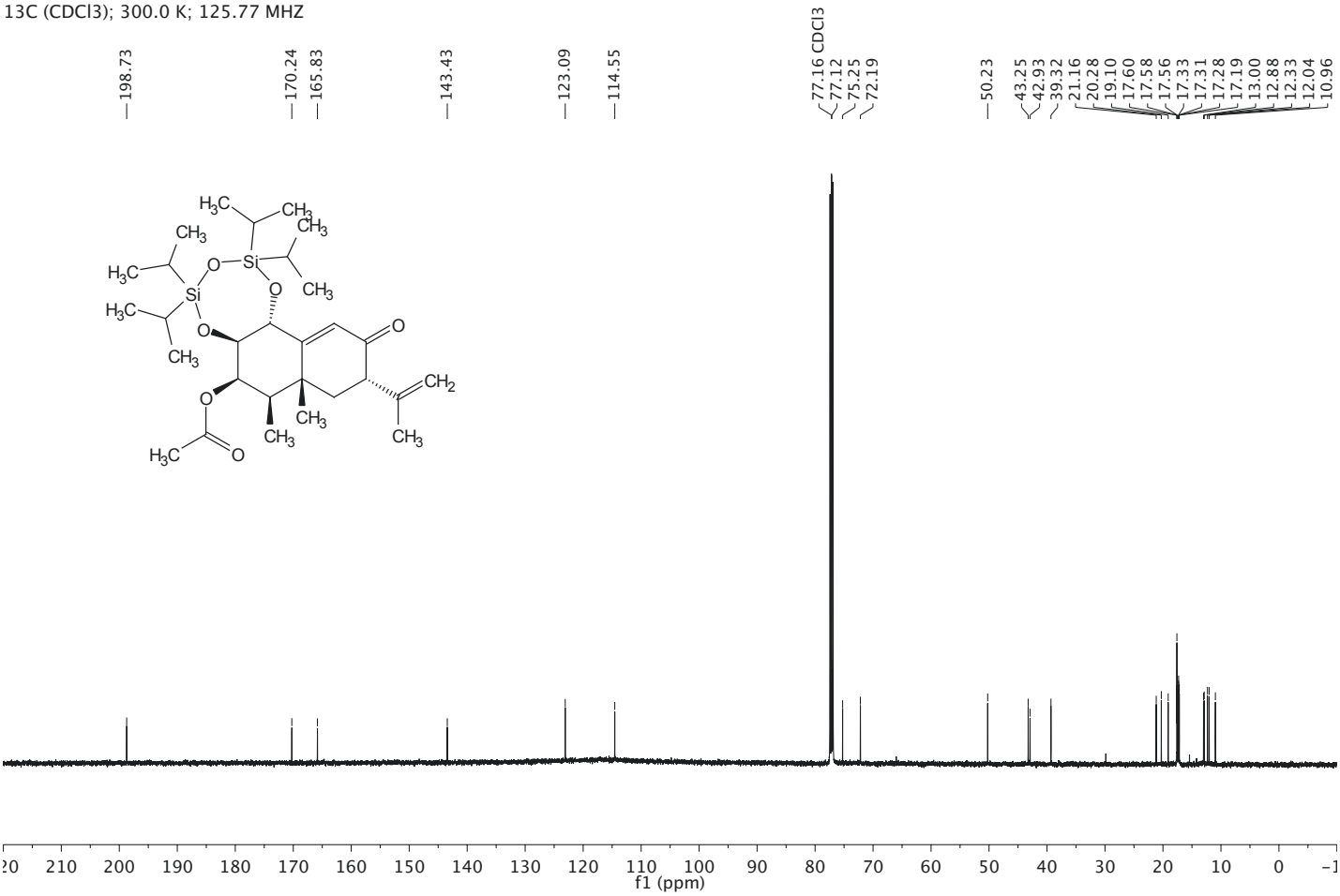
13C (CDCl3); 300.1 K; 125.80 MHZ



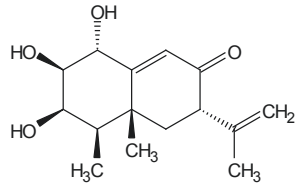
1H (CDCl3); 299.9 K; 500.13 MHZ



13C (CDCl3); 300.0 K; 125.77 MHZ



1H (MeOD); 298.0 K; 500.13 MHZ

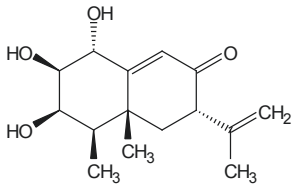


6.20
6.20
4.93
4.81
4.49
4.47
3.86
3.40
3.37
3.31 CD2HOD
3.26
3.23
2.00
1.97
1.88
1.70
1.53
1.49
1.41
1.15
1.13

0.89
1.25
1.11
0.93
0.97
0.97
1.06
0.98
1.04
2.90
1.01
2.96
3.00

f1 (ppm)

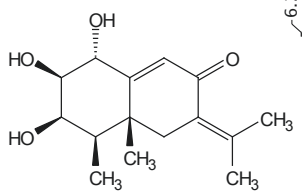
13C (MeOD); 300.0 K; 125.81 MHZ



201.66
172.62
144.90
121.97
114.69
77.44
75.59
70.09
51.27
45.85
44.37
40.83
20.22
19.75
11.81

f1 (ppm)

1H (MeOD); 299.9 K; 500.30 MHZ

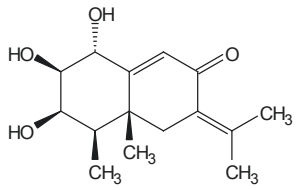


6.20
6.20
4.44
4.43
3.86
3.39
3.37
3.31 CD2HOD
2.99
2.96
2.13
2.10
2.08
2.07
1.89
1.88
1.56
1.55
1.18
1.18
1.17

0.87
1.00
1.06
1.33
0.98
1.16
2.97
3.04
1.03
3.03
2.97

f1 (ppm)

13C (MeOD); 300.0 K; 125.81 MHZ



194.19
171.28
145.54
128.65
124.19
77.56
75.64
70.08
49.00 CD3OD
44.76
43.65
43.06
22.84
22.39
20.11
12.09

f1 (ppm)